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Supreme Court, U.S.
FILED

09-792 DEC 28 2009

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No.

In The

Supreme Court of the United States

THOMAS REMPFER,

Petitioner

v.

MARGARET HAMBURG, M.D.,
COMMISSIONER, U.S. FOOD & DRUG ADMINISTRATION,
ET AL.

Respondents

On Petition For Writ Of Certiorari To The United States Court of Appeals for the District of Columbia

PETITION FOR WRIT OF CERTIORARI

LT. COL. THOMAS REMPFER
Pro Se
6058 South Jakemp Trail
Tucson, AZ 85747
(520) 869-6590

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Questions Presented for Review

In 1998, the United States Department of Defense (DoD) ordered members to receive the anthrax vaccine. Many soldiers declined the order because they believed the vaccine was not properly licensed by the Food and Drug Administration (FDA). The matter percolated in the lower courts for the past decade as members challenged the legality of mandatory vaccinations in civilian and military forums. The 10-year history of lower court litigation notably includes injunctions in 2003 and 2004 by the District Court for D.C. The Court's 2004 summary judgment halted mandatory vaccinations on the grounds that the vaccine was not properly licensed. In 2005, the FDA completed the licensure process. The Plaintiff in this matter contests the presumed legality of the 2005 licensure based on a lack of evidence that the vaccine is effective against inhaled anthrax. This background presents the following questions for the Court's review:

> *First*, when military orders hinge on the legality of a final administrative action of a non-military agency, can members of the armed forces contest the propriety of the non-military agency's action?

> *Second*, where ethical concerns preclude adequate human clinical trials, what level of evidence is necessary for the FDA to license a biologic product, such as a vaccine?

Parties to Proceeding

Petitioner: Lt. Col. Thomas Rempfer.

Respondents: Margaret Hamburg, M.D., Commissioner, U.S. Food & Drug Administration; Robert Gates, Secretary of Defense; Kathleen Sebelius, Secretary of Health and Human Services.

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Text of Petition

Citations to Decisions Below

1. *Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Anthrax Vaccine Adsorbed; Final Order*, 70 F.R. 75180 (FDA, Dec. 19, 2005).
2. *Rempfer v. Von Eschenbach*, 535 F. Supp. 2d 99 (D.D.C. 2008) (Appendix 1).
3. *Rempfer v. Sharfstein*, 583 F.3d 860 (D.C. Cir. 2009) (Appendix 2).

Jurisdiction:

Review is sought from the decision of the Circuit Court of Appeals for the District of Columbia, dated September 29, 2009 (Appendix 1). The District Court for the District of Columbia filed its final decision in this matter on February 29, 2008 (Appendix 2). The final agency action at issue was published in the Federal Register by the U.S. Food & Drug Administration on December 19, 2005.

This Court has jurisdiction pursuant to 28 U.S.C. § 1254. The Circuit Court had jurisdiction pursuant to 28 U.S.C. § 1291. The District Court had jurisdiction pursuant to 5 U.S.C. § 702, 28 U.S.C. §§ 2201, 1331 and 1346.

Statutes

1. When a drug has not yet been licensed by the FDA, the consent of the recipient is normally

required before it can be administered. 21 U.S.C. 355(i)(4):

> **(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary**
>
> **(1)** The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—
>
> ....
>
> **(4)** Regulations under paragraph (1) shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where it is not feasible or it is contrary to the best

> interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs. The Secretary shall update such regulations to require inclusion in the informed consent documents and process a statement that clinical trial information for such clinical investigation has been or will be submitted for inclusion in the registry data bank pursuant to subsection (j) of section 282 of title 42.

2. When the military seeks to use a non-licensed drug, the military has the authority to administer it to service members in connection with a particular military operation, if the service members consent, or if the president waives the consent requirement. [1] 10 U.S.C. § 1107(f)(1):

> In the case of the administration of an investigational new drug or a drug unapproved for its applied use to a member of the armed forces in connection with the member's participation in a particular military operation, the requirement that the member provide prior consent to receive the drug in accordance with the prior consent requirement imposed under section 505(i)(4) of the Federal

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[1] The President issued an Executive Order in 1999 that effectively embodies the same standard. *Improving Health Protection of Military Personnel Participating in Particular Military Operations*, Executive Order 13139 (Sept. 30, 1999).

> Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)) may be waived only by the President. The President may grant such a waiver only if the President determines, in writing, that obtaining consent is not in the interests of national security.

3. When the normally required two adequate, controlled human clinical studies are not available, a drug can be licensed based on only one such study, if there is sufficient confirmatory evidence. 21 U.S.C. § 355(d):

> **(d) Grounds for refusing application; approval of application; "substantial evidence" defined**
>
> If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that ....
>
> (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations,

> including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.

Statement

In 1998 the military began its Anthrax Vaccine Immunization Program ("AVIP") to inoculate service members in certain theaters against the threat of aerosolized anthrax.[2] The only "approved" anthrax vaccine available in the United States, then and now, is called Anthrax Vaccine Adsorbed ("AVA," or "the vaccine"). AVA was tested in the 1950's during a

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[2] Cohen, W. (1998). *Implementation of the Anthrax Vaccination Program for the Total Force.* Retrieved from http://www.anthrax.mil/documents/902implementationpolicy.pdf

DoD sponsored field trial[3] for use by tannery workers handling raw, potentially anthrax infected hides. Dr. Phillip S. Brachman executed this 1957 human clinical trial for AVA for the DoD.[4] During the study approximately 26 workers out of the 1,249 studied were infected with anthrax; the great majority were from cutaneous, or skin exposure, with only five or so believed to have been infected by inhaled anthrax. Though the government granted a license, during the process regulators noted a failure to submit the required "scientific evidence for efficacy of the vaccine." The Centers for Disease Control (CDC) specifically challenged the licensing application at that time due to the absence of proper efficacy data. In the 1990s, the vaccine underwent "major," DoD coordinated manufacturing changes according to the Government Accountability Office (GAO) (Appendix 3).[5] The manufacturing alterations were not approved until over a decade later, and without additional clinical trials. According to the GAO, the alterations required prior approval and the manufacturer failed to report some of the major changes to the FDA. Regardless of the modifications, the Brachman study remains the seminal source of proof regarding efficacy of the new, altered vaccine,

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[3] Brachman, P., Plotkin, S., Bumford, F., & Atchison, M. (1960). An epidemic of inhalation anthrax: the first in the twentieth century. II. Epidemiology. *American Journal of Hygiene*, July (72), 6-23.

[4] Brachman, P., Gold, H., Plotkin, S., Fekety, F., Werrin, M., & Ingraham, N. (1962, April). Field Evaluation of a Human Anthrax Vaccine. *American Journal of Public Health*, 52(4), 632-645.

[5] GAO-02-181T. (2001, October). *Anthrax Vaccine: changes to the manufacturing process.* Appendix 2.

and serves as the prime basis for FDA licensure under FDA Comparability Policy Guidance.[6]

Significantly, following the aforementioned unapproved manufacturing alterations, but before the pivotal FDA licensure at issue in this filing, earlier manufacturing quality control problems[7] remained unresolved until "expedited" agency action ensued following the "Amerithrax" anthrax letter attacks. Only recently, the Federal Bureau of Investigation (FBI) associated these known testing irregularities of the existing vaccine to the 2001 anthrax letter attacks. The FBI alleged a DoD scientist's motive stemmed from the fact that the "anthrax vaccine he was working on was failing" due to potency problems, which the scientist was responsible for resolving.[8] The GAO reported that

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[6] *Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products.* (1996). Retrieved from http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm

[7] FDA Notice of Intent to Revoke. (1997). In Food and Drug Administration (Ed.), *CBER Warns Michigan Biologic Products Institute of Intention to Revoke Licenses.* Retrieved from http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/default.htm; http://www.fda.gov/cber/infosheets/mich-inf.htm; http://www.fda.gov/NewsEvents/Testimony/ucm114911.htm

[8] Note: The DoD scientist worried in the timeframe preceding the letter attacks, "I think the **** is about to hit the fan...bigtime. The final lot ... isn't passing the potency test, and now there's nothing to back it up. Plus, the control vaccine isn't working ... It's just a fine mess." (2008, August 6). Federal Bureau of Investigation, *Amerithrax Court Documents.* Retrieved from http://www.usdoj.gov/amerithrax/; http://www.usdoj.gov/opa/documents/opa-080806.html; http://www.usdoj.gov/opa/pr/2008/August/08-opa-697.html; http://www.usdoj.gov/amerithrax/docs/07-524-m-01.pdf

manufacturing changes might have resulted in up to a "hundredfold increase" in potency attributes.[9]

As argued below, and as the District Court in D.C. held in 2003, beyond the manufacturing problems AVA was also never properly licensed for use against inhaled anthrax before the 2005 Final Rule. *See Doe v. Rumsfeld*, 297 F.Supp.2d 119, 131 (D.D.C. 2003), *appeal dis'd as moot*, 172 Fed. Appx. 327 (D.C. Cir. 2006). It is critical to understand that in the decades following the Brachman study, its deficiencies (principally but not wholly related to small sample size and the insignificant number of inhaled anthrax cases) were consistently noted by those who considered the matter, including government scientists. Repeated comments were made, including by Brachman himself, that the 1957 study did not sufficiently establish the efficacy of AVA against inhaled, vs. cutaneous anthrax infection. In fact, with the assistance of the DoD, the vaccine manufacturer in 1996 filed an Investigational New Drug ("IND") application to seek licensure for "inhalation anthrax." Yet, during this timeframe, the 1985 Proposed Rule for licensure languished un-finalized, while comments critical of the AVA in general, and specifically as a treatment for inhaled anthrax, continued to mount.

As demonstrated above and further below, the most significant new development driving the vaccine's ultimate licensure for inhaled anthrax in 2005 was political and bureaucratic, rather than new scientific or medical evidence. These dynamics included the advent of the AVIP in 1998, and were further motivated by the post-2001 anthrax letter attack atmosphere. After the 1998 to 2001 moment

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[9] Ibid at 5, nn. 5-13.

of pivot, the executive branch of the U.S. Government, notably the Department of Defense ("DoD") and the Food and Drug Administration ("FDA"), purported to reexamine the Brachman data and claimed to find therein new evidence for efficacy, specifically for inhaled, aerosolized or inhalation anthrax. As part of the about-face, the government apparently altered its previous official position, one identical to that of the present petitioner, *i.e.*, that the DoD needed a new vaccine due to the efficacy limitations of AVA. The DoD published this requirement in a Request for Proposal (RFP) for a new vaccine as early as 1985.[10] Also published in 1985, the FDA's Proposed Rule[11] for anthrax vaccine similarly expressed the fundamental position of this petitioner, *i.e.*, that "no meaningful assessment of [AVA's] value against inhalation anthrax is possible." Following implementation of the DoD AVIP, and the anthrax letter attacks, the government asserted that the older 1970 NIH licensure, promulgated prior to

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[10] DoD-Request for Proposal (RFP) (see Admin Record). (1985, May 16). *Request for Proposals for new anthrax vaccine by US Army Medical Research Acquisition Activity*. (No. DAMD 17-85-R-0078 ed.). Fort Detrick, Frederick, MD. The RFP stated, "There is an operational requirement to develop a safe and effective product which will protect US troops against exposure from virulent strains of Bacillus anthracis." The RFP added, "There is no vaccine in current use which will safely and effectively protect military personnel against exposure to this hazardous bacterial agent." The RFP clarified that the current vaccine is, "highly reactogenic [reactive], requires multiple boosters to maintain immunity and may not be protective against all strains of the anthrax bacillus."

[11] A 1985 FDA Advisory Panel published a proposed rule in the Federal Register in order to finalize the anthrax vaccine's license. The Proposed Rule noted the "efficacy against inhalation anthrax is not well documented." 50 F.R. 51002 (Dec. 13,1985).

FDA's assumption of vaccine responsibilities in 1972, sufficiently included the use of the vaccine for inhalation anthrax. The FDA altered the earlier understood limited use of the vaccine for at risk individuals against cutaneous anthrax, which had stood for some 30 years, instead broadening the license for all routes of exposure.

When the D.C. District Court agreed in late 2003 that the vaccine had never been licensed for inhaled anthrax, the government eight days later in January 2004, finally acted on the pending 1985 Proposed Rule, granting the license for AVA and added efficacy for inhalation anthrax. *Doe v. Rumsfeld*, 297 F.Supp.2d at 131. The District Court then stepped in, holding that the 2004 licensure was inadequate under the Administrative Procedures Act, 5 U.S.C. §§ 511-99, enjoining the AVIP unless and until a license based on proper procedures was issued. In 2005, the government issued a new Final Rule following a comment period, again relying in large part on the Brachman study. Notably, Dr. Brachman, in post-licensure writings, cites government conclusions that AVA is effective against inhaled anthrax, whereas the FDA relies primarily on his study.[12] Dr. Brachman's reluctance to assert directly the efficacy of the vaccine based on his 1957 clinical trial, as relied upon by the FDA, exemplifies an unsuitable circular chain of reasoning that renders the FDA decision arbitrary and capricious.

While the government was preparing to issue its final licensure order in 2005, it simultaneously

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[12] Brachman, P., Friedlander, A., & Grabenstein, J. (2008). Anthrax Vaccine, Chapter 8. In S. Plotkin, W. Orenstein & P. Offit (Eds.), *Vaccines* (5th ed., pp. 111-124). Philadelphia, Pa.: Saunders/Elsevier.

appealed the District Court's injunction. FDA ultimately issued a new Final Rule in December 2005, and because of this new Final Rule, the court dismissed the appeal on grounds of mootness in February 2006. Therefore, the Court of Appeals never reviewed the merits of the vaccine's final licensure for inhalational anthrax in 2005; that question is the gravamen here. With the injunction dissolved, DoD Undersecretary Dr. David Chu ordered renewed mandatory military vaccinations.[13] Ironically, Dr. Chu previously recommended DoD "minimize" AVA use immediately prior to the controversial anthrax letter attacks in 2001.[14] DoD recommendations to minimize use of the anthrax vaccine, rely on antibiotics, and develop a new vaccine placed the old vaccine in jeopardy. The anthrax letter attacks apparently were motivated to resolve this previous "failing" status of the program, and essentially led to the current dispute over licensure and continued reliance on AVA.[15]

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[13] Chu, D. (2005, April 29). *DoD Implementation of Resumption of the Anthrax Vaccine Immunization Program.*

[14] Chu, D., & Aldridge, P. (2001, August 10). In Rumsfeld D. *Technology Development for Force Health Protection Against Biological Threat*, RE minimizing anthrax vaccine. Retrieved from http://www.fda.gov/ohrms/dockets/dockets/80n0208/80N-0208_emc-000192-07.pdf. Available in docket & Admin Record.

[15] Ibid at 8, p. 15. AVA's use significantly expanded to include over $1 billion in procurement for the nation's Strategic National Stockpile after the letter attacks. The procurements represented a major leap compared to the vaccine's problems revealed through FBI released emails. The DoD scientist's admitted that the vaccine "isn't passing the potency test." The emails stated, "If it doesn't pass ... the program will come to a halt." The FBI confirmed, the FDA "had suspended further production" because the "same vaccine was having problems in the production phase." Ultimately, the DoD awarded the DoD

As with this Petitioner, many similarly situated service members in all branches of the armed forces were disciplined for refusing the vaccine, based on orders issued both before and after the district court injunction. It is worth noting that many members were disciplined before the 2003 court order confirmed that the vaccine was not properly licensed; those punishments were never lifted or ameliorated, even after the mandatory vaccination program was enjoined by a court finding that the vaccine was not properly licensed exactly as these service members had argued. This is in the face of clear statutory requirements, discussed further below, that consent (or a presidential waiver of consent) is required when the military seeks to administer an unlicensed treatment to its members. Also of note, during this entire period, the Court of Appeals for the Armed Forces (CAAF) periodically faced the identical issue of the legitimacy of the vaccine licensure by FDA. The CAAF essentially accepted at face value the government's assertion that the vaccine had been properly licensed at all times since 1970. *United States v. Kisala*, 64 M.J. 50 (C.A.A.F. 2006).

This is contrary to the decisions of the D.C. District Court, the same opinion the D.C. Court of Appeals declined to vacate. The CAAF also held that military orders were presumed legal. The practical result in this case being that so long as government makes a colorable assertion that a drug is properly licensed, service members cannot question the final administrative action of a non-military agency (such as the drug's licensure here), even if their military

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scientist, Dr. Bruce Ivins, the highest honor for "getting the anthrax vaccine back into production." The FBI found, "with respect to the motive" and the "troubled nature of Dr. Ivins" related to "concern about the end of the vaccination program."

orders are based on such a final administrative action. The CAAF noted this conflict with the approach taken in the federal courts in D.C. *Kisala*, 64 M.J. 50.

In the matter at bar, where service members contest the vaccine's 2005 licensure, the Court of Appeals carried through with the 2003 District Court's different approach to the issue of proper licensing; that is to say, the Court of Appeals completed a full merits review of the FDA's licensing process without questioning the service member's right to contest an agency action, even when that agency action underpins military orders. *See Rempfer v. Sharfstein*, 583 F.3d 860 (D.C. Cir. 2009).

Reasons for Granting the Petition

The Petitioner's basic legal claim relies on the official documented position previously held by the DoD and its scientists involved with anthrax vaccine prior to the advent of the politically charged AVIP and the letter attacks. Those attacks were allegedly launched to overcome the fundamental failings of the vaccine, its potency and efficacy problems, and make for the premise of the Petitioner's claim for review. The resultant arguments supporting this claim borrow from scholarly articles, logic and commonsense in asserting the necessity to resurvey the entire scheme:

> First, the anthrax vaccine is not FDA-approved because of alterations in its chemical formula and a change in its intended use from the original vaccine. As such, the FDA must consider it an IND ["Investigational New Drug" per 21 U.S.C. § 355(i)(4)]. Second, since the

> vaccine is an IND, it requires informed consent of the service member under federal law and a Presidential Executive Order. Third, since the current vaccine is illegal to administer and was administered without consent, the order directing the service member to become vaccinated was illegal.[16]

Fourth, Dr. Brachman's study historically was not considered a reliable means of proving efficacy for inhalation anthrax according to the author himself. Instead, today Dr. Brachman points not to his earlier study, but to the *government's* conclusions, in asserting the efficaciousness of AVA. Circularly though, those government conclusions by the FDA and the National Academies of Science Institute of Medicine (IOM) point back to Dr. Brachman's study for proof of efficacy. IOM acknowledges AVA is "far from optimal" and advises a "new vaccine, developed according to more modern principles of vaccinology, is urgently needed." [17]

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[16] RANDALL J. KATZ, *Friendly Fire: The Mandatory Military Anthrax Vaccination Program*, 50 Duke L.J. 1835, 1852-53 (2001) (citations omitted). Additional scholarly analysis on the AVIP exists in peer-reviewed literature: Corrigan, S. (2001). *Total Force Anthrax Vaccine Immunization Program: Controversy and Conflagration*. Harvard Law School. Retrieved from http://leda.law.harvard.edu/leda/data/365/Corrigan.pdf;

[17] IOM. (2002, April). *The anthrax vaccine: Is it safe? Does it work?* Institute of Medicine (U.S.). Committee to Assess the Safety and Efficacy of the Anthrax Vaccine. Washington, D.C: National Academy Press, p. 208. Earlier IOM reports cautioned, "There is a paucity of published peer-reviewed literature on the safety of the anthrax vaccine." IOM. (2000, March 30). An assessment of the safety of the anthrax vaccine [electronic resource]: a letter report. Committee on Health Effects Associated with Exposures during the Gulf War.

Each of the abovementioned reasons stand contrary to the DoD's planned August 2001 minimization of anthrax vaccine use due to its "failing" status and the "political problems" related to "Gulf War Syndrome."[18] The Petitioner reasons that the reversal resulted from AVA's illegal use and the anthrax letter attacks plan to "save" the AVIP, leading directly to improper agency action and unwarranted court acquiescence in the matter at bar.

I. Circuit Split

The two most important courts in the nation for determining the validity of military orders that hinge on the legality of an underlying final administrative action of a non-military agency are divided in that the CAAF has in effect stated that when a military order is based on an administrative order from a non-military agency, the legality of the underlying administrative action is entitled to the same heavy presumption of legality that applies to military orders. In contrast, the civilian federal courts in the District of Columbia, as exemplified in the matter at bar, have moved directly to a review of the merits of the civilian agency's actions on the arbitrary and capricious standard of review, without any consideration of the presumption of legality of military orders. *Compare Rempfer*, 583 F.3d 860, *with Kisala*, 64 M.J. 50.

Institute of Medicine (U.S.). Washington D.C: Institute of Medicine, p. 6. Retrieved from http://books.nap.edu/openbook.php?record_id=9811&page=R1

[18] Ibid at 14, and Rove, K. (2001, April 25). In Deputy Secretary of Defense Wolfowitz P. (Ed.), Gulf War Syndrome and Anthrax (See Appendix 9). Retrieved from http://www.mvrd.org/rovememo.pdf

The CAAF's approach at bottom is that if a civilian agency so much as colorably asserts that it has taken a final, legal action on which a subsequent military order depends, the CAAF needs conduct no further review of the propriety of the agency's actions, but rather moves straight to an analysis based on the presumption of legality of military orders. In contrast, civilian courts in the matter at bar have addressed the merits of the question whether the 2005 licensure (or any earlier iteration thereof) is valid. The CAAF has instead stated in effect that since the FDA has asserted that the anthrax license has been in place since 1970, the CAAF can presume that the agency action is legal and need not inquire into the merits of the agency action, either as to the original licensure in the 1970's for cutaneous anthrax, or the latest licensure in 2005 for inhaled anthrax. The practical question is should civilian courts apply the presumption of legality of military orders when they review challenges to the legality of civilian agency administrative actions by members of the military who assert they are subject to illegal orders? Or, should the courts under the Armed Forces jurisdiction review the validity of a civilian agency order before they apply the presumption of legality of military orders?

The Court of Appeals for the D.C. Circuit is the nation's leading administrative law forum outside of this Court, while the Court of Appeals for the Armed Forces is the nation's foremost lower court authority on military matters, exercising worldwide appellate jurisdiction over members of the armed services on active duty and others subject to the Uniform Code of Military Justice in a wide variety of civil and criminal matters. It is highly undesirable for these

two crucial forums to disagree on an important issue at the intersection of their zones of expertise and influence – the proper weight, if any, to be given to final orders of a non-military administrative agency when military orders hinge on the legality of such final orders. *Kisala*, 64 M.J. 50.

The court with administrative law expertise did not address the issue of the presumed legality of military orders, while the court with military expertise relied on the presumption of legality of military orders to the exclusion of an appropriately rigorous review of the legality of the administrative action. This may be a case of ships passing in the night, unaware of each other's presence, mission and import – and thus presents an opportunity for this Court to exercise its responsibility to draw together and unify two disparate legal approaches to the same fundamental and important problem: to what extent, if any, can members of the military contest the validity of final non-military agency decisions when such decisions underpin a military order.

The CAAF itself acknowledges this important difference in approach, wherein the federal courts in D.C. did not examine the presumed legality of the military orders that the petitioners were subjected to:

> The federal district court's evaluation of the civil remedies differs from our evaluation of the criminal charges that arise in the military context of Appellant's willful disobedience of a presumed lawful order. The linchpin of this case is the presumed legality of the military order to receive the Vaccine. The district court opinions neither

> recognize nor address this critical presumption.

Kisala, 64 M.J. at 53.[19]

This presents a grave anomaly that only this Court can remedy: It is inconsistent for one service member, who is not facing criminal charges, to be able to contest the legality of a final agency action in civilian court, while another service member who is being criminally prosecuted for disobeying an identical military order does not have the opportunity to contest the exact same agency action. *See United States v. New*, 55 M.J. 95, 105 (C.A.A.F. 2001) (the "word 'lawful' [in the provision regarding the presumed legality of military orders] simply reinforces the opportunity for the accused to challenge the validity of the regulation or order with respect to a superior source of law without establishing a separate and distinct element of the offense").[20]

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[19] One court has gone even further, and declared that the DoD's assertion that the anthrax vaccine was properly licensed constitutes a nonjusticiable political question. See *Perry v. Wesely*, No. NMCM 200001397, 2000 WL 1775249, at *3 n.2 (N-M. Ct. Crim. App. Nov. 29, 2000) ("Complicating the inquiry in the petitioner's case is his effort to contest the lawfulness of the commanding officer's order by litigating the legality of the DoD anthrax vaccination program itself, a nonjusticiable political decision").

[20] The standard of review of final agency administrative actions, such as the anthrax licensure here, is arbitrary and capricious. A military order hinging on an arbitrary and capricious agency action would seem to be patently illegal. Therefore, at this petition for certiorari stage, consistency is desirable in the various forums when service members assert that a military order is not lawful because it is premised on an illegal administrative agency action, such as the FDA's final anthrax vaccine licensure decision here.

This disparity in the two forums' handling of alleged violations of similar military orders is rendered all the more urgent and ripe for review by the fact that the court using the more restrictive approach, here the CAAF, is using the more stringent standard in *criminal* cases. This is akin to a state's allowing speeders who are facing merely civil sanctions such as driver's license suspensions to contest the inspection and calibration of the state police radar guns, while imposing a presumption that the radar guns are accurate on speeders who are charged criminally. This Court should accept this matter for review to resolve the inconsistency between these two courts on an important issue.[21]

II. Case Involves Urgent National Security Problem That Will Recur, With Open Legal Issue In Need of Clarification

This Court needs no reminding that a new century has dawned with terrorism and unprecedented national security threats presenting hitherto unseen challenges to the legal system, including threats posed by Weapons of Mass Destruction ("WMD") – biological, chemical and nuclear threats that can be levied against both military and civilian targets. Anthrax is clearly one such weapon – and the national security and legal challenge posed when the government tries to protect its military and its citizens against threats such as

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[21] For other examples of the military courts' consistent approach of not reviewing the vaccine's licensure on the merits, see *United States v. Schwartz*, 61 M.J. 567 (U.S. Navy-Marine Corps Ct. Crim. App. 2005); *Ponder v. Stone*, 54 M.J. 613 (U.S. Navy-Marine Corps Ct. Crim. App. 2000); see also, Katz, 50 DUKE L.J. at 1852.

anthrax can unfortunately be expected to be repeated as new WMD threats emerge. It is appropriate and desirable for the nation in facing such threats to have clear legal guidance from this Court in place when future threats arise from some unexpected quarter – an unknown pathogen or other WMD developed by terrorists. In this instance, the government's attempt to prepare for and protect against the anthrax threat relies on an old medication, one that languished without final agency action for decades because of its seeming obscurity, limited scope or use, and obsolescence. As well, administrative inertia appeared to prevail, caused by the understanding of all concerned about the inadequacy of the scientific evidence of the vaccine's efficacy, its potency problems, and the failure to synthesize long sought alternatives to this inadequate vaccine.

The next time, the unlicensed treatment might not be an old and forgotten one, but rather a new one developed using the most modern methods, but perhaps created on the fly to meet an urgent need. In either case, the legal issue that will be presented when the military once again needs to use unlicensed treatments on its members is the same: from a legal standpoint, what requirements must be met before the military can administer an unlicensed treatment without seeking the recipients' consent or a presidential waiver of consent?

The question is made all the more proper for this Court's attention and current clarification because of the special concern that these issues may arise in the future on an emergency, urgent basis as the nation and its military, medical and regulatory institutions scramble to address an unforeseen threat. It will be far better for this Court to have considered these

matters in the more deliberate manner presented by this case, rather than on a crisis basis.

This Court should exercise its discretionary and supervisory authority to hear this matter in order to provide a solid, clear and workable legal framework for the nation's civil and military commanders. Additionally, individual members of the armed forces, who serve patriotically, deserve to know with clarity what legal rights they do – and do not – have with respect to unlicensed drugs or other treatments that might be mandated.

This problem raises important issues of national security and personal liberty that are within the historic purview of this Court, and currently the civilian and military justice arenas are taking different, yet universally deferential approaches.

The question of course has broader applicability than just the particular FDA and drug licensure order at issue here; it rather applies whenever a final administrative decision of a civilian agency underlies military orders, and affected service members contest the legality of the civilian agency's final action.

III. The Result Below Creates an Injustice

Without suggesting that the injustice being worked against is alone enough to merit a grant of certiorari, it is nevertheless important for the Court to understand that petitioner here belongs to a class of honorable, hard-working, honest and in many cases distinguished members of the armed services who suffered consequences including discipline, transfers (voluntary and involuntary), delayed or denied promotion, and other personal, professional, and emotional harms as a consequence of attempts to

honor the highest and most difficult traditions of duty in military service – questioning in good faith the legality of an order received. These injuries have not been remedied or alleviated in any way – despite the indisputable fact that the fundamental claim that this vaccine was not properly licensed at the outset of the mandatory vaccination program in 1998 was accepted by no less of an authority than the District Court for D.C. Moreover, the federal government, since the time of that District Court decision, has proceeded as if it were in full agreement that the vaccine was never properly licensed for inhalational anthrax exposure until late 2005.

That is to say, to this day many service members continue to be injured based on their refusal of orders to take the vaccine – while the government can and does argue that post-2005 refusals are not appropriate, it is hard to make a fair case for any disciplinary or other sanctions based on pre-2005 refusals. This assessment is validated not just by the District Court's decision in unrelated *Doe v. Rumsfeld* matters in 2003 and 2005, but also by the behavior of the Defense Department, who punished the plaintiffs for arguing that the vaccine was not licensed for inhaled anthrax. Meanwhile, the DoD and FDA at the same time proceeded to secure a license for the anthrax vaccine for inhalational indications. The bottom line is that this country has punished, and continues to punish, certain of its faithful warriors for a dutiful stance they took at a time when even the government (*i.e.*, as illustrated by its own subsequent actions of pursuing and securing a final license) now concedes the vaccine was not properly licensed for the purpose the military wished to use it for. This injustice alone

may not make this case worthy of *certiorari*, but it is a fair point to mention.

a. **Scorecard: Pre-1998 v. Post-1998**

Before the military's anthrax vaccination program launched in 1998, the scientific and administrative commentary on the safety and efficacy of the vaccine was consistently negative. The pre-program commentary also consistently recognized that the vaccine was not proven effective against inhaled anthrax.[22] After the

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[22] Examples of pre-1998 commentary regarding AVA:

- "When inhalation anthrax is considered, the limited experience with this form of the disease makes the data less significant in showing effectiveness of the vaccine" (Brachman, P., Gold, H., Plotkin, S., Fekety, F., Werrin, M., & Ingraham, N. (1962, April). Field Evaluation of a Human Anthrax Vaccine. *American Journal of Public Health*, 52(4), p. 642.;
- "No data on MDPH-PA [anthrax vaccine] efficacy in humans" existed (Ivins, B. (1992, October 6). In Deputy Commander, MDPH-PA vaccine efficacy in humans. p. 2);
- DOD scientists described the vaccine as an "experimental," "limited use vaccine" (Takafuji, E., & Russell, P. (1990). *Military immunizations. Past, present, and future prospects*. Infectious Disease Clinics of North America, 4(1), p.156;
- "Current vaccines, particularly the anthrax vaccine, do not readily lend themselves to use in mass troop immunization [because of], in some cases, lack of strong enough efficacy against infection by the aerosol route" (Congress - S.Hrg. 101-744. (1989, February 10). Hearing on the Global Spread of Chemical and Biological Weapon, RE DoD Letter to Sen. Glenn, (Aug. 24,1989));
- Anthrax vaccine "drawbacks, including the need for frequent boosters, the apparent inability to protect adequately against certain strains of B. anthracis, and occasional local reactogenicity" (Ivins, B. (1988) The search for a new-generation human anthrax vaccine. *Clinical Immunology Newsletter*, 9(2), 30-32);

anthrax vaccine was made the center of a military initiative in 1998, the government dramatically changed course, and began arguing that no separate licensure for inhalational anthrax was needed, regardless of the fact an unapproved IND application existed. This sea change was captured in an amicus brief filed by the Connecticut Attorney General in the D.C. Circuit in 2005 in the *Doe v. Rumsfeld* litigation discussed elsewhere (Appendix 4):

> Before the federal government decided to "cut corners" and violate the requirements of 10 U.S.C. § 1107, everyone agreed that there was insufficient data on the safety and efficacy of the anthrax vaccine with respect to inhalation anthrax. The FDA, the author of the study, the DoD, the CDC and the manufacturer all agreed and acted on the basis that the vaccine was an [Investigational New Drug, that is to say, unlicensed] with respect to inhalation anthrax.

Amicus Brief of the Connecticut Attorney General, dated August 11, 2005 at 6 (hereafter, "AG Brief) (Appendix 4).

It is likely that the government in its responsive filing will marshal examples of favorable commentary on AVA's effectiveness, and perhaps

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➢ "Unsatisfactory" nature of the current product due to unknown purity, undefined nature, undesirable constituents and efficacy issues (Brachman, P., & Friedlander, A. (1994). Anthrax, Chapter 26. In S. A. Plotkin, & E. A. Mortimer (Eds.), *Vaccines* (2nd ed., pp. 773-996). Brachman, P., & Friedlander, A. (1998). Anthrax, Chapter 24. In S. Plotkin, & W. Orenstein (Eds.), *Vaccines* (3rd ed., pp. 629-636)).

statements supportive of the judgment that no separate licensure for inhalational anthrax is needed. The Court should keep a scorecard when reading the respondents' (or Judge Garland's) list of positive AVA comments: how many of the government's positive scientific citations come from before 1998 vs. how many come in or after 1998? That, of course, being the year when the anthrax vaccine program was launched, and also the year when the government ceased being a neutral, sideline observer, adjudicator, and regulator of AVA, and rather became the first large user of the anthrax vaccine ever, with a huge vested interest in having the vaccine legalized.

This Petitioner asks the Court to consider what happens when the government stops being the regulator – and becomes the applicant?

b. Scorecard: Executive Branch v. Others

Another important metric the Court should keep its eye on: both before and after 1998, institutions other than the executive branch of the U.S. Government have consistently criticized the vaccine's efficacy and/or the adequacy of the purportedly seminal Brachman study. This includes strong criticism of the vaccine and its fitness for mandatory administration from both other branches of the federal government, as well as from state governments. [23] This is not to say that in the exercise

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[23] Critical commentary from outside the executive branch:

➢ In 1994, a Senate Committee Report found, "the vaccine's effectiveness against inhaled anthrax is unknown," and therefore should be "considered investigational when used as a protection against biological warfare." (Congress - SR 103-97. (1994, December 8). 103-2. *Is Military Research hazardous*

of diligence the government will not reveal positive commentary from credible institutions outside the executive branch, or not funded or otherwise linked to the executive branch; but we predict a lopsided score, with positive comments coming principally from the executive branch or its dependents and connections.

IV. Decisions Below Were in Error

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to Veteran's Health?: Lessons Spanning Half a Century, p. 35., see Admin Record).

- Later Congressional reports concurred stating, "use of the current anthrax vaccine for force protection against biological warfare should be considered experimental and undertaken only pursuant to FDA regulations governing investigational testing for a new indication." Congressional investigations also revealed DoD awareness that the "potency test required for the present vaccine has not been well correlated to efficacy in humans and it is doubtful that it can be" (Congress - HR 106-556. (2000, April 3). *Unproven Force Protection*, pp. 4, 52, 62. fn. 269. Washington, DC: GPO.
- GAO reports also confirmed that the "the vaccine and the manufacturing process were changed;" that the "ingredients used to make vaccine were changed from the original vaccine," and that "prior to the time of licensing, no human efficacy testing of the MDPH vaccine was performed" (GAO T-NSIAD-99-148. (1999, April). *Medical readiness: safety and efficacy of the Anthrax vaccine*, p. 1-3.
- CT Att. Gen.: "Suddenly in 1997, DoD and the FDA, with no change in the facts or the law, reversed themselves and with the stroke of a pen wiped out the protections afforded our members of the Armed Services by clearing the way for DoD's mandatory mass inoculations." (Blumenthal, R. (2001, March 22). In Rumsfeld D., Schwetz B. (Eds.), Letters from the Connecticut Attorney General to DoD and FDA "RE: ANTHRAX VACCINE." Retrieved from http://www.ct.gov/ag/cwp/view.asp?A=1776&Q=283330; http://www.ct.gov/ag/lib/ag/press_releases/2001/health/dod.pdf; http://www.ct.gov/ag/lib/ag/press_releases/2001/health/fda.pdf)

Both the FDA and Judge Garland premise their finding that the anthrax vaccine here was properly licensed on the hypothesis that the vaccine is as effective against inhaled anthrax as it is against cutaneous anthrax. The scientific evidence, including much evidence produced by the government itself (FDA, CDC and DoD) prior to the initiation of the government's own use of the vaccine in 1998, does not support this hypothesis, and if *certiorari* is granted here, close scrutiny will show that any such finding is arbitrary and capricious.

This is not a case involving the adequacy of a drug license against a private party; here, the entity seeking to declare the licensure valid, and seeking to use the vaccine, is the licensing authority: the FDA. Normally, when a drug license is in question, the federal government and the FDA are in a position something like a neutral referee between two non-government parties; but here, the government itself is the entity asserting that it should be allowed to use this drug because its licensing process was valid. This Court should view this matter in the context of FDA and DoD, perhaps understandably, fighting to save an executive branch initiative in which they played an intimate role.

a. **Judge Garland's Unwitting Approach**

Again, while the errors may not alone merit this Court's attention, they bear mention. We do not take issue with Judge Garland's statement that:

> At bottom, the plaintiffs' claim that the Brachman Study establishes nothing in regard to "inhalational anthrax" relies on the proposition that route of exposure is scientifically relevant. But the FDA's

> contrary determination is a scientific judgment within its "area of expertise," the kind of judgment to which this court gives a "high level of deference."

(Decision at 12.)

However, here the FDA's errors are fundamental; and they were moreover perpetuated and magnified by Judge Garland. Judge Garland repeatedly revealed a fundamental misunderstanding of the judiciary's appropriate role in reviewing the validity of the FDA's finding that the vaccine here was proven to be effective as a matter of scientific evidence. Specifically, Judge Garland, rather than simply assessing the adequacy of the evidence relied on by FDA, repeatedly – and apparently in all good faith and unwittingly – relies on his own scientific judgments *en route* to his conclusion that the FDA's decision was not so unmoored from scientific basis as to be arbitrary and capricious.

For instance, when Judge Garland states:

> But this simply directs us to the underlying issue: should "inhalational anthrax" be analyzed separately? That question cannot, as appellants assume, be answered as an abstract question of statistical method. Rather, it must be answered as a matter of scientific judgment. To illustrate: if the *route*-of-exposure distinction were replaced with a *time*-of-exposure distinction, no one would insist that "morning anthrax" must be analyzed separately from "afternoon anthrax." Yet categorizing cases by time seems arbitrary not because time of exposure is

> any less measurable a distinction than route of exposure, but because time seems unlikely -- as a scientific matter -- to be relevant to vaccine effectiveness.

(Decision at 10), he has based his thinking on a scientific assumption of his own creation – the idea that time of exposure is "unlikely to be relevant." (*Ibid.*) The point here is not whether or not Judge Garland's (or FDA's) scientific assumption that time of exposure does not matter is incorrect – FDA's judgment if well-grounded is entitled to "high deference." Rather, Judge Garland's time-of-exposure thought experiment is not based on any evidence in the record – it is a scientific assumption or hypothesis (as it turns out an incorrect one, see footnote) by a lawyer who is in all good faith trying to exercise what he takes to be common sense; it is arbitrary and capricious. [24]

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[24] Judge Garland's hypothesis – that time of exposure is never relevant – is incorrect when considering bacterial and viral infections generally, and probably incorrect regarding anthrax. Substantial evidence exists that the time of exposure, levels of sunlight, and ambient temperature may impact infection rates. Scientific literature includes references to such variables as a factor in infection with respect to many pathogesn. *See, e.g.*, Cyril William Holmes, *Black's Medical Dictionary* (Harvard 1990) at 71 (tuberculosis); El-Ayyat Afaf A; Sayed Hanan A; El-Desoky Howaida H., *Pattern of water contact activities in relation to S. mansoni infection in rural area in Giza Governorate, Egypt*, J. EGYPT PUBLIC HEALTH ASSOC. 2003, 78 (5-6): 417-32 (schistomiasis); Reuters Health News, *Factors associated with persistence of hepatitis C viremia identified* (April 1, 1999) (hepatitis C) (discussing Patrick G. Quinn, AM. J. GASTROENTEROLOGY 1999;94:668-673 (April 1, 1999)). With specific reference to anthrax, the scientific literature from its beginnings has noted sunlight's role in impeding anthrax., *e.g.*, "In subsequent experiments with sunlight, Arloing found that two hours of exposure to the July

Judge Garland's assertion that "no one would insist that 'morning anthrax' must be analyzed separately from 'afternoon anthrax'" shows at once a serious lack of understanding of the scientific method, as well as a failure to grasp the scientific specifics of the matter at hand. Judge Garland's own conclusion, that "categorizing cases by time seems arbitrary not because time of exposure is any less measurable a distinction than route of exposure, but because time seems unlikely -- as a scientific matter -- to be relevant to vaccine effectiveness" does more than any skilled advocate ever could to demonstrate an unwitting abdication of the proper prudentially limited role of the judicial system in reviewing the FDA's scientific judgment.

A judge's role is not to decide whether or not time of exposure, or route of exposure, is likely or unlikely to be relevant. It is not for him, or this Court, to judge what factors are, or are not, arbitrary or unlikely to be relevant as a scientific matter; it is rather for the judiciary to satisfy itself that the government reviewed the scientific evidence and literature in a way that was not arbitrary and not capricious – that is, the proper subject for court review is whether or not the government followed the

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sun sufficed to destroy the vitality of anthrax spores .... Cultures which were weakened in their reproductive energy by exposure to sunlight were also 'attenuated' as to their pathogenic power ...." GEORGE MILLER STERNBERG, A MANUAL OF BACTERIOLOGY, (William Wood & Co. 1893) at p. 152; accord, Holmes at 71. Other complex factors play into whether or not a pathogen is successful in penetrating the body, for instance body temperature, recent stress, having other infections, and normal circadian rhythms. An entire field called chronobiology has emerged in recent years. Sharon M. Miller, *About Time: A Chronobiological Approach to Healthcare*, 28 MEDICAL LABORATORY OBSERVER, 26 (January 1, 1996).

science without being misleading or dishonest, and also without falling into Judge Garland's own more innocent mistake of unconsciously relying on subjective assumptions in reviewing the FDA's analysis.

The FDA repeats Judge Garland's fundamental errors of method at several crucial junctures. For instance, Judge Garland highlights the FDA Final Rule's conclusion that, "*Thus, AVA elicits an antibody response to disrupt the cytotoxic effects of toxins produced by anthrax bacteria, regardless of the route of infection.* 2005 Final Rule, 70 Fed. Reg. at 75,187 (emphasis added)," and adds his explanation: "[i]n other words, AVA responds to anthrax in the same way regardless of how the disease enters the body."

The assumption underlying Judge Garland's and the FDA's reasoning in that instance is that because "toxins produced by anthrax bacteria do not vary based on the route of exposure," and it is demonstrable that the AVA vaccine attacks toxins, it is valid to conclude that route of exposure does not matter. That is incorrect. The FDA in this passage cites two measurable pieces of scientific data: 1. that the toxins produced by anthrax which enters the body through the skin are the same as the toxins produced by anthrax which enters the body through the lungs; and 2. that the vaccine attacks those toxins. This is an analysis on the cellular/molecular level, and is fine as far as it goes. What is missing is any evidence comparing the course of the disease outside of the level of the toxins produced by the bacteria, at the level of the infected individual's body. For instance, are there differences in toxin dispersal and distribution throughout the body,

based on the route of infection? Or, in dispersal and distribution throughout the human body of the bacteria itself (not the toxin)? Or in the rate of the anthrax organism's reproduction and proliferation in different host tissues? Or, in the amount of toxin produced by anthrax hosted in different types of tissues?

Even the FDA does to an extent acknowledge issues of this sort, stating "We agree that the route of exposure to an infectious agent may potentially have an impact on the effectiveness of a vaccine. The impact likely depends on the nature of the infectious agent in terms of its mechanism of virulence and the pathophysiology of infection and disease, and the mechanism of protection afforded by the vaccine" 70 F.R. at 75187. But then the FDA, in its usual post-1998 pattern, goes on to declare that the Brachman study provides sufficient answers for this. *Id.*

Before turning to a brief review of other flaws in the FDA's reasoning and processes, a word needs to be said about the unusual context in which the FDA was forced to conduct its review, followed by the final licensing in 2005 of a drug that had languished virtually unused on the dusty back shelves of the nation's apothecary for the better part of half a century – with a corresponding lack of regulatory activity or oversight by FDA and its predecessors. The Court needs to be aware that unusual outside pressures have seriously impacted the normal, low-key scientific process here. The FDA and the DoD at all times since 1998 have been on an urgent mission to "save" the anthrax vaccine program, and to protect presidents from both parties from the need to sign a

declaration waiving the consent requirement.[25] Clearly, any president from 1998 forward could have definitively halted the controversy, anxiety and professional difficulties imposed on thousands of government scientists, administrators, military commanders, and service members, not to mention halted an enormous body of unnecessary litigation including this case, by simply declaring that a waiver of the personal consent pursuant to 10 U.S.C. § 1107 was in the national interest. [26] This petitioner and many others would have understood and obeyed the president's invocation of the proper legal process to mandate inoculation of military personnel with an unlicensed vaccine. Instead, the executive branch never chose to follow the lawful procedure laid down by Congress to address such exigencies.

The motivation of the FDA and the DOD in many regards here is commendable: to protect the military and the nation against a serious threat that has emerged in recent years. But the scramble to save the vaccine has led to short-cuts, unsound scientific evaluations, and unhealthy rulemaking precedents.

b. Circular Reasoning

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[25] Defense Secretary Rumsfeld, at an October 18, 2001 news conference, commented on the AVIP & AVA: "We're going to try and save it. ... it may or may not be savable." Retrieved from http://www.defense.gov/Transcripts/Transcript.aspx?TranscriptID=2130

[26] *Ibid.* at 8. The unusual pressure government scientists were under is illustrated by the FBI report concluding that the 2001 anthrax-by-mail killer was most likely one of the government's leading anthrax scientists, possibly driven in part by concerns that the critics of the anthrax vaccine's safety, efficacy, and licensing shortcomings were gaining traction.

The government, in its attempts to seize a final licensure after the setbacks and injunctions imposed by the D.C. district court between 2003-05, tries to argue that it has much more evidence than just the flawed Brachman study. But a close review does not bear that out; rather, the FDA's supposedly non-Brachman evidence itself relies on Brachman's 1957 epidemic study. Here are the steps: later work by Brachman and his colleagues, in order to overcome the challenge posed by the District Court's 2003 and 2004 decisions and injunctions, point to FDA and IOM; but those supposedly additional sources of evidence both explicitly and heavily rely on the results of Brachman's 1957 study. FDA procedures and federal statutes require two adequate, controlled human studies.[27] If we assume for a moment that the Brachman study with its shortcomings even qualifies as one adequate human study, the FDA would still need to meet the requirement in 21 U.S.C. § 355(d)(7) for substantial "confirmatory evidence," to bolster the results of the one study. It defies logic, and the FDA's rules, to allow the confirmatory evidence *to be itself substantially based on the single available study*. The law allows the FDA to deviate from the normal drug-licensure requirement of two clinical trials; but wisely requires confirmatory evidence. That evidence should not stem from a single human clinical trial questioned by its own author, or perhaps from studies published by the

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[27] The FDA states, "as a general rule, two adequate and well-controlled studies are needed to prove the product's safety and effectiveness." *FDA Backgrounder, The FDA Modernization Act of 1997* (Nov. 21, 1997). The statutes allow FDA to rely on only a single human controlled study in some instances, but requires substantial confirmatory evidence when only one human clinical trial is available. *See, e.g.*, 21 U.S.C. § 355(d)(7).

alleged letter attack perpetrator as cited in the FDA's 2005 Final Rule for AVA.[28]

c. **FDA's Other Errors**

It is not the intent of this document to contest the merits on an item-by-item basis. The two preceding subsections (a.) and (b.) rather seek to raise errors of fundamental methodology. In this subsection, we note very briefly a number of other errors by the FDA. Judge Garland's propensity to bake unexamined (and possibly incorrect) hypotheses and assumptions into his review of the FDA's decision making is replayed throughout his decision, as well as the FDA's own review.

Ignored are the FDA improperly approved major manufacturing changes to the vaccine, as well as the DoD's orchestration of a 1996 license application for inhaled anthrax. Other serious failings exist that could be developed in depth during a merits review of this matter, any one of which might support a finding that the FDA order was arbitrary and capricious. They include changes to AVA's dosage schedule and the route of administration (i.e., subcutaneous vs. intramuscular), *see, e.g.* 21 C.F.R. § 312, again triggering the consent provisions of 11 U.S.C. § 1107.

In sum, over the years the FDA and DoD significantly altered the vaccine, its manufacturing process, the dosage schedule, and the route of administration as they saw fit or found convenient, without regard for the regulations that trigger IND status and potentially new clinical trials, thus

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[28] Ivins cited in AVA 2005 Final Rule70 F.R. at _____, nn. 3-5.

requiring consent of military recipients. The sum effect of these actions, and the lower court's misplaced deference, represents a clear indication of arbitrariness and caprice that warrants review.

Conclusion

The Court should grant review in order to resolve a significant split in the lower courts: criminal defendants in the CAAF who refused anthrax vaccine are subject to conviction and penalties up to and including incarceration with no opportunity to contest the legality of the FDA licensing rule that underpins the military command to take the vaccine; whereas plaintiffs in the civilian courts who contest the legality of the same rule are afforded the opportunity to contest the agency action on its merits. This appears unjust and unwise when evaluating challenges to military orders.

A second issue worthy of the Court's review concerns the level of evidence needed before the FDA can license a drug where ethical concerns preclude adequately controlled human clinical trials. Here, only one half-a-century old human clinical trial exists, using a different vaccine, after major subsequent manufacturing alterations. Moreover, the licensure review must be viewed in the unusual context where the Executive Branch of the government had a vested interest in this vaccine's license, instead of acting in its normal role as a neutral administrative arbiter. Here, the entity evaluating the legality of the license also defended its licensure and significantly expanded its use through the civilian Strategic National Stockpile following the 2001 bioterrorism events.

This Petitioner respectfully requests the Court review AVA's license based on the abovementioned arguments, as well as the prescient relevancy of the anthrax letter attacks and the DoD's deleterious affect on FDA approval methodologies.

Respectfully submitted,

/s/

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DECEMBER 28, 2009

Appendixes

Appendix 1 – Court of Appeals Opinion

United States Court of Appeals

For the District of Columbia Circuit

Argued April 20, 2009

Decided September 29, 2009

No. 08-5117

THOMAS REMPFER,

U.S. AIR FORCE, ET AL., APPELLANTS

v.

JOSHUA M. SHARFSTEIN, MD, ACTING COMMISSIONER, FOOD AND DRUG ADMINISTRATION, ET AL., APPELLEES

Appeal from the United States District Court for the District of Columbia

(No. 1:06-cv-02131-RMC)

John J. Michels Jr. argued the cause for appellants. With him on the briefs was Mark S. Zaid.

Melissa N. Patterson, Attorney, U.S. Department of Justice, argued the cause for appellees. With her on the brief were Michael F. Hertz, Acting Assistant Attorney General, Jeffrey A. Taylor, U.S. Attorney, and Mark B. Stern, Attorney. R. Craig Lawrence, Assistant U.S. Attorney, entered an appearance.

Before: HENDERSON, TATEL, and GARLAND, Circuit Judges.

Opinion for the Court filed by Circuit Judge GARLAND.

GARLAND, Circuit Judge: Pursuant to the Department of Defense's Anthrax Vaccine Immunization Program, members of the armed forces may be ordered to submit to inoculation against anthrax disease. Eight servicemembers brought suit in district court to challenge the Food and Drug Administration's approval of the anthrax vaccine and to enjoin the Defense Department from administering it. The district court dismissed three counts of the complaint on the merits and dismissed a fourth count because the plaintiffs lack standing to make it. We affirm.

I

Anthrax is an acute bacterial disease caused by infection with spores of Bacillus anthracis. It can be contracted through three routes of exposure: by skin contact (cutaneously), by inhalation, and by ingestion. From 1954-1959, a clinical study led by Dr. Philip Brachman tested an anthrax vaccine produced by the Department of Defense (DOD). See Philip S. Brachman et al., Field Evaluation of a Human Anthrax Vaccine, 52 AM. J. PUB. HEALTH 632 (1962) [hereinafter Brachman Study]. Dr. Brachman studied 1249 textile workers exposed to imported goat hair, dividing the population into a vaccine group, a placebo group, and an observational (no treatment) group. Id. at 634, 638.

[1] During the study, 26 cases of anthrax

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[1] As the FDA explained: The Brachman Study's "selected population was at risk because the mill workers routinely handled anthrax-infected animal materials. Prior to

occurred: 21 contracted cutaneously and 5 by inhalation. Id. at 638. Three of the cutaneous cases occurred in the vaccine group; the remainder, and all inhalation cases, occurred in the placebo and observational groups. Id. The study calculated that the vaccine was 92.5 percent effective (lower 95 percent confidence limit = 65 percent). Id. at 644. The study noted, however, that the small number of inhalation cases "makes the data less significant in showing effectiveness of the vaccine" with respect to that "form of the disease." Id. at 643.

DOD subsequently contracted with Merck, Sharpe, & Dohme to develop a new version of the vaccine for large-scale production. See Food and Drug Administration (FDA), Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Anthrax Vaccine Adsorbed; Final Rule, 70 Fed. Reg. 75,180, 75,192 (Dec. 19, 2005) [hereinafter 2005 Final Rule]. Later, it entered into a similar contract with the Michigan Department of Public Health (MDPH), the relevant division of

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vaccination, the yearly average number of human anthrax infections among workers in these mills was 1.2 cases per every 100 employees." Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Anthrax Vaccine Adsorbed; Final Order, 70 Fed. Reg. 75,180, 75,186 (Dec. 19, 2005). By the mid-1980s, this industrial setting was "vanishing, precluding any further clinical studies." Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review, 50 Fed. Reg. 51,002, 51,058 (Dec. 13, 1985). Today, "due to the significant health risks associated with exposure to anthrax spores, it would not be ethical to actively expose human study subjects to B. anthracis spores in order to assess the effectiveness of an anthrax vaccine in a controlled clinical trial. Furthermore, naturally occurring anthrax is now so rare that a field study of vaccine effectiveness is no longer feasible in the United States." 70 Fed. Reg. at 75,192.

which is now operated by the BioPort Corporation. Id. at 75,181, 75,182, 75,192, 75,197. MDPH/BioPort produced and continues to produce the current generation of the vaccine, known as Anthrax Vaccine Adsorbed (AVA). Id. at 75,192.

Prior to 1972, the National Institutes of Health (NIH) was the agency responsible for the licensing of biological products. See 2005 Final Order, 70 Fed. Reg. at 75,181. In 1970, NIH issued a license for AVA. As labeled, the vaccine was to be administered in a six-shot sequence, with specified intervals between each inoculation. Id. at 75,184.

In 1972, responsibility for licensing biological products was transferred from NIH to the FDA. Id. at 75,181. The FDA then issued procedures for determining that products previously licensed by NIH "are safe, effective, and not misbranded." Procedures for Review of Safety, Effectiveness and Labeling, 38 Fed. Reg. 4319, 4321 (Feb. 13, 1973) (codified as amended at 21 C.F.R. § 601.25). Under those procedures, the FDA appoints an independent advisory panel to report on covered products. See 21 C.F.R. § 601.25(a), (e). After reviewing the panel's recommendations, the FDA makes its own determination, which it publishes as a Proposed Order along with the panel's report. See id. § 601.25(f). After receiving and reviewing comments, the FDA publishes a final order. See id. § 601.25(g).

In 1973, the FDA announced that advisory panels would review the safety and effectiveness of several vaccines previously licensed by NIH, including AVA. Biological Products; Bacterial Vaccines and Toxoids with Standards of Potency, Single or in Combination; Safety, Effectiveness and

Labeling Review; Request for Data Information, 38 Fed. Reg. 5358 (Feb. 28, 1973). In 1980, an advisory panel submitted a report finding that the "best evidence for the efficacy of anthrax vaccine comes from [the] placebo-controlled field trial conducted by Brachman." Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review, 50 Fed. Reg. 51,002, 51,058 (Dec. 13, 1985). Although the panel concluded that "inhalation anthrax occurred too infrequently [in the Brachman Study] to assess the protective effect of vaccine against this form of the disease," it recommended categorizing AVA as "safe and effective under the limited circumstances for which [it] is employed." Id. at 51,058, 51,059. In 1985, the FDA issued a Proposed Order classifying AVA as "safe and effective and not misbranded," id. at 51,104, but it did not issue a final order, see 2005 Final Order, 70 Fed. Reg. at 75,182.

In 1998, DOD implemented the Anthrax Vaccine Immunization Program (AVIP), which subjected members of the Armed Forces at risk of anthrax exposure to mandatory administration of AVA. See id. at 75,183. Thereafter, Congress directed DOD to support an independent examination of AVA by the Institute of Medicine of the National Academy of Sciences. Id.; see H.R. Rep. No. 106-371, at 256 (1999) (Conf. Rep.). A committee convened by the Institute conducted the study, examined "all available data," and concluded that, "[a]s indicated by evidence from studies in both humans and animals,...AVA, as licensed, is an effective vaccine to protect humans against anthrax, including inhalational anthrax." COMM. TO ASSESS THE SAFETY AND EFFICACY OF THE ANTHRAX VACCINE, INSTITUTE OF MEDICINE, THE

ANTHRAX VACCINE: IS IT SAFE? DOES IT WORK? 1-2 (2002) (J.A. 140-41) [hereinafter Institute of Medicine Report].

Meanwhile, in July 2000, a shortage of the vaccine resulted in a temporary suspension of DOD's vaccination program, causing servicemembers who had begun the six-dose regimen to miss scheduled shots. First Am. Compl. ¶¶ 58, 59, 61; Rempfer v. Von Eschenbach, 535 F. Supp. 2d 99, 111 (D.D.C. 2008). According to the plaintiffs, when the suspension ended in 2002, DOD announced that personnel whose vaccination series had been interrupted would not repeat any doses already received but would instead continue with the next dose in the series. First Am. Compl. ¶¶ 63-64.

Six servicemembers sought to enjoin the vaccination program in 2003. Doe v. Rumsfeld, 297 F. Supp. 2d 119, 123, 130 (D.D.C. 2003). Although they did not dispute that AVA had been approved as safe and effective against cutaneous anthrax, they argued that it was not a licensed vaccine for inhalational anthrax. Id. As a consequence, they maintained, 10 U.S.C. § 1107(f)(1) barred administration of the vaccine without either informed consent or a Presidential waiver.[2]

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[2] The statute provides:

> In the case of the administration of an investigational new drug or a drug unapproved for its applied use to a member of the armed forces in connection with the member's participation in a particular military operation, the requirement that the member provide prior consent to receive the drug in accordance with the prior consent requirement imposed under section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)) may be waived only

Finding a likelihood of success on this claim, the district court issued the requested preliminary injunction in December 2003. Doe, 297 F. Supp. 2d at 135. Days later, the FDA finalized the order it had proposed in 1985, but revised it to specify that AVA was safe and effective "independent of the route of exposure." Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review, 69 Fed. Reg. 255, 260, 257-59 (Jan. 5, 2004). The district court vacated that order for failure to comply with the notice-and-comment requirements of the Administrative Procedure Act (APA), 5 U.S.C. § 553. Doe v. Rumsfeld, 341 F. Supp. 2d 1 (D.D.C. 2004). The court then issued a permanent injunction -- "unless and until FDA follows the correct procedures to certify AVA" as safe and effective -- against "involuntary anthrax vaccinations absent informed consent or a Presidential waiver." Id. at 16. The government filed an appeal in this court.

In December 2004, the FDA issued a new proposed order for comment. Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review, 69 Fed. Reg. 78,281 (Dec. 29, 2004). After reviewing the comments, the FDA issued a new final order on December 19, 2005, again classifying AVA as safe and effective in the prevention of anthrax regardless of the route of exposure. 2005 Final Order, 70 Fed. Reg. 75,180. In February 2006, a panel of this court concluded that, because issuance of the new order caused the permanent injunction to

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by the President. The President may grant such a waiver only if the President determines, in writing, that obtaining consent is not in the interests of national security.

10 U.S.C. § 1107(f)(1).

dissolve "[b]y its own terms," the government's appeal was moot. Doe v. Rumsfeld, 172 Fed. Appx. 327, 328 (D.C. Cir. 2006). In October 2006, DOD announced resumption of the mandatory immunization program. First Am. Compl. ¶ 8.

Thereafter, the plaintiffs in the case now before us – eight servicemembers subject to mandatory inoculation orders -- initiated new proceedings in the district court challenging the FDA's 2005 final order. First Am. Compl. ¶¶ 1-8. They also sought to enjoin DOD from deviating from the recommended six-shot schedule for servicemembers whose vaccinations DOD had suspended between 2000 and 2002. The plaintiffs alleged that any such deviation would violate 10 U.S.C. § 1107(f)(1). Id. ¶¶ 102-12; see supra note 2. The district court resolved the only issue raised by the plaintiffs' three claims against the FDA -- whether the agency's reliance on the Brachman Study to establish the vaccine's effectiveness against anthrax was arbitrary or capricious under the APA -- in favor of the agency. Rempfer, 535 F. Supp. 2d 99. It also dismissed the plaintiffs' claim against DOD for lack of standing based on the plaintiffs' failure to allege that they had been or would be subjected to off-schedule inoculations. Id.

We review the district court's APA ruling de novo, "as if the agency's decision 'had been appealed to this court directly.'" Gerber v. Norton, 294 F.3d 173, 178 (D.C. Cir. 2002) (quoting Dr. Pepper/Seven-Up Cos. v. FTC, 991 F.2d 859, 862 (D.C. Cir. 1993)). We also review de novo the district court's dismissal of the claim against DOD for lack of standing. Muir v. Navy Fed. Credit Union, 529 F.3d 1100, 1105 (D.C. Cir. 2008).

II

The plaintiffs' principal challenge is to the FDA's determination that the anthrax vaccine is effective.[3] More specifically, they fault the FDA's reliance on the Brachman Study in making that determination. They argue that reliance on that study was improper because: 1) it cannot support a finding of effectiveness against anthrax contracted by inhalation; and 2) it cannot support a finding of effectiveness for the current generation of the anthrax vaccine. The plaintiffs do not contest the vaccine's safety.

We will consider both arguments, but first pause to correct the plaintiffs' misperception regarding the nature of the district court's review, and of ours, under the APA. The plaintiffs repeatedly insist that the district court was obliged to deny the government's motion to dismiss because they had raised genuine issues of material fact and hence were entitled to discovery to flesh out their claims. But "when a party seeks review of agency action under the APA [before a district court], the district judge sits as an appellate tribunal." Am. Bioscience, Inc. v. Thompson, 269 F.3d 1077, 1083 (D.C. Cir. 2001). "The entire case on review is a question of law," and the "complaint, properly read, actually presents no factual allegations, but rather only arguments about the legal conclusion to be drawn about the agency

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[3] "Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological product, when used under adequate directions, for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man." 21 C.F.R. § 601.25(d)(2).

action." Marshall County Health Care Auth. v. Shalala, 988 F.2d 1221, 1226 (D.C. Cir. 1993).[4] Consequently, challengers are "not . . . ordinarily entitled to augment the agency's record with either discovery or testimony presented in the district court," and there is "no inherent barrier to reaching the merits" at the motion to dismiss stage. Id. Our review, like that of the district court, is based on the agency record and limited to determining whether the agency acted arbitrarily or capriciously. See 5 U.S.C. § 706.

A

The plaintiffs first object that, because the Brachman Study included few cases of anthrax contracted by inhalation, it cannot support a conclusion of effectiveness against that route of exposure. We grant the plaintiffs' premise but disagree with their conclusion.

The FDA does not dispute that, if "the cases of inhalation anthrax reported in the course of the Brachman study [are] analyzed separately, [they] are too few to support a meaningful statistical conclusion." 2005 Final Order, 70 Fed. Reg. at 75,183. But this simply directs us to the underlying issue: should "inhalational anthrax" be analyzed separately? That question cannot, as appellants assume, be answered as an abstract question of

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[4] See *Am. Bioscience*, 269 F.3d at 1083 (noting that, "when reviewing agency action[,] the question of whether the agency acted in an arbitrary and capricious manner is a legal one which the district court can resolve on the agency record, regardless of whether it is presented in the context of a motion for judgment on the pleadings or in a motion for summary judgment").

statistical method. Rather, it must be answered as a matter of scientific judgment. To illustrate: if the route-of-exposure distinction were replaced with a time-of exposure distinction, no one would insist that "morning anthrax" must be analyzed separately from "afternoon anthrax." Yet categorizing cases by time seems arbitrary not because time of exposure is any less measurable a distinction than route of exposure, but because time seems unlikely -- as a scientific matter -- to be relevant to vaccine effectiveness.

Of course, in comparison to time of exposure, it is not as self-evident that route of exposure is unlikely to be relevant. After all, Dr. Brachman did flag the route-of-exposure distinction half a century ago. Moreover, the FDA agrees that, as a general matter, "the route of exposure to an infectious agent may potentially have an impact on the effectiveness of a vaccine." Id. at 75,187.

But in the case of the anthrax vaccine, the FDA's scientific judgment is that route of exposure is not relevant to the vaccine's effectiveness. The reason, the agency explains, is as follows:

With regard to the known pathophysiology of anthrax, the signs and symptoms of disease arise due to the production of toxins by anthrax bacteria growing within the infected individual. The toxins produced by anthrax bacteria do not vary based on the route of exposure. The antibodies produced in response to vaccination contribute to the protection of the vaccinated individual by neutralizing the activities of those toxins. Thus, AVA elicits an antibody response to disrupt the cytotoxic effects of toxins produced by anthrax bacteria, regardless of the route of infection.

2005 Final Order, 70 Fed. Reg. at 75,187 (emphasis added). In other words, AVA responds to anthrax in the same way regardless of how the disease enters the body. Thus, for purposes of establishing AVA's effectiveness, the inhalational versus cutaneous distinction is one without a difference, and there is no need to treat them separately in interpreting the Brachman Study. This, the FDA explains, is why it disagrees with the 1980 advisory panel's statement that inhalation anthrax occurred too infrequently in the Brachman Study to provide a basis for assessing the efficacy of AVA against that form of the disease. Id. at 75,183; see 38 Fed. Reg. at 4321 (stating that "the report of each panel is advisory to the Commissioner, who has the final authority to accept or to reject the conclusions and recommendations of the panel").

As the FDA further notes, its judgment in this respect is in accord with the report of the committee of experts charged by the Institute of Medicine with conducting an independent review. 2005 Final Order, 70 Fed. Reg. at 75,183. The committee found that "laboratory experiments indicate that AVA provides effective protection against inhalational challenge in rabbits and macaques, the animal models in which the disease is most reflective of the disease in humans." Institute of Medicine Report, at 10. And the committee concluded that, "[a]s indicated by evidence from studies in both humans and animals, ...AVA, as licensed, is an effective vaccine to protect humans against anthrax, including inhalational anthrax." Id. at 2.[5]

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[5] The FDA found additional support for the effectiveness of the vaccine in epidemiological data "on the occurrence of

At bottom, the plaintiffs' claim that the Brachman Study establishes nothing in regard to "inhalational anthrax" relies on the proposition that route of exposure is scientifically relevant. But the FDA's contrary determination is a scientific judgment within its "area of expertise," the kind of judgment to which this court gives a "high level of deference." A.L. Pharma, Inc. v. Shalala, 62 F.3d 1484, 1490 (D.C. Cir. 1995); see Serono Labs., Inc. v. Shalala, 158 F.3d 1313, 1320 (D.C. Cir. 1998). Moreover, as the plaintiffs themselves concede, there is no scientific evidence in the administrative record to contradict that judgment. See Oral Argument Recording at 35:03.[6] In the absence of such evidence, we must defer to the FDA's judgment that AVA is effective regardless of the route of exposure.

B

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anthrax disease in at-risk industrial settings collected by the [Centers for Disease Control and Prevention] and summarized for the years 1962 to 1974." 2005 Final Order, 70 Fed. Reg. at 75,183. The FDA noted that unvaccinated persons within the at-risk populations had been infected by anthrax during that period, but that "no cases have occurred in fully vaccinated subjects while the risk of infection has continued." Id.

[6] At oral argument, plaintiffs' counsel pointed to one piece of evidence purportedly contradicting the FDA's judgment – a declaration the plaintiffs filed in the district court. See J.A. 212. The declaration was not submitted to the FDA during the administrative proceedings and was not mentioned in the plaintiffs' appellate briefs. It is therefore outside the scope of our review on two accounts. See Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 420 (1971) (holding that review is generally limited to the "record that was before the [agency] at the time [it] made [its] decision"); Ark Las Vegas Rest. Corp. v. NLRB, 334 F.3d 99, 108 n.4 (D.C. Cir. 2003) (holding that arguments raised for the first time at oral argument are waived).

The plaintiffs' other principal contention is that, because the Brachman Study used an earlier generation of the anthrax vaccine, it cannot establish the effectiveness of the current version. We again grant the premise but reject the conclusion.

The fact that manufacturing changes occur during the course of vaccine production is not unique to AVA, and the FDA has an established protocol for analyzing such changes: "[A] manufacturer may make manufacturing changes in a product without performing additional clinical studies to demonstrate the safety and effectiveness of the similar product if data regarding the manufacturing changes support the conclusion that the versions are comparable." 2005 Final Order, 70 Fed. Reg. at 75,184. The plaintiffs maintain that "there is no evidence within the Administrative Record that the FDA ever compared the different anthrax vaccines and efficacy data to reach the conclusion that the vaccines are comparable." Appellants' Br. 43. But that is simply incorrect, because the FDA did make the requisite comparability determination.

As the FDA explained in its 2005 Final Order, it "reviewed the historical development of AVA and conclude[d] that DOD directed the development of the vaccine, including its formulation and manufacturing process, from the vaccine used in the Brachman study . . . to the vaccine that was ultimately licensed and manufactured by BioPort." 2005 Final Order, 70 Fed. Reg. at 75,184. "All three versions of anthrax vaccine," the agency determined, "were tested in animals and demonstrated to protect test animals . . . against challenge with virulent [anthrax] spores." Id. In addition, "clinical data comparing the safety and immunogenicity of [AVA]

with [the DOD] vaccine...reveal that the serological responses to [AVA] and [the DOD] vaccine were similar with respect to peak antibody response and seropositivity." Id. That is, human blood serum showed similar antibody production in response to the different versions of the vaccine. Id. at 75,184, 75,192-93. The FDA also found that the two versions were "comparable in their ability to protect test animals." Id. at 75,184. On this basis, the agency concluded that the two vaccines were comparable and that the Brachman Study could therefore be used to approve AVA. Id.

Once again, we are presented with a scientific judgment by the FDA to which we owe considerable deference. And once again, the plaintiffs fail to proffer any scientific evidence to rebut it. Our conclusion must therefore be the same as above: the FDA did not act arbitrarily or capriciously in resting a finding of effectiveness on the results of the Brachman Study.[7]

III

Finally, we address the plaintiffs' claim that DOD is subjecting military personnel to mandatory immunization on an unapproved schedule of inoculations. The district court dismissed this claim on the ground that the plaintiffs lack standing to

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[7] Scattered throughout the plaintiffs' briefs are a number of additional arguments criticizing the Brachman Study. Because those arguments are raised "only summarily, without explanation or reasoning," they are waived. *City of Waukesha v. EPA*, 320 F.3d 228, 251 n.22 (D.C. Cir. 2003). In any event, we agree with the carefully considered opinion of the district court that those additional challenges lack merit. See Rempfer, 535 F. Supp. 2d at 108-11.

raise it. "To establish constitutional standing, a plaintiff must show an injury in fact that is fairly traceable to the challenged conduct and that will likely be redressed by a favorable decision on the merits." Muir, 529 F.3d at 1105 (citing Lujan v. Defenders of Wildlife, 504 U.S. 555, 560-61 (1992)). The district court concluded that the plaintiffs have not alleged the constitutionally requisite injury in fact, and we agree.

The plaintiffs' complaint alleges that DOD began its program of mandatory inoculation in 1998, suspended it for some period during 2000-02 due to a supply shortage, and then resumed the program without correcting for the interruption in the recommended six-shot dosage schedule. First Am. Compl. ¶¶ 10, 58-64. The plaintiffs do not allege that servicemembers who were or will be inoculated for the first time under the post-2002 regime will have their inoculations interrupted and restarted off schedule. Nor do they claim that DOD is otherwise stopping and restarting the shot sequences. Rather, they allege that "'[p]ersonnel whose vaccination series was interrupted during the p[re]vious AVIP slowdown....will just continue with the next dose in the series.'" First Am. Compl. ¶ 63 (emphasis added) (quoting an Air Force statement).

As the district court noted, the plaintiffs have "not alleged that they themselves have been, or imminently will be, subjected to such [an interrupted] vaccination schedule." Rempfer, 535 F. Supp. 2d at 111. The complaint does not allege that the inoculation sequence of any of the plaintiffs was actually interrupted by the 2000-02 AVIP suspension. Nor have the plaintiffs filed an affidavit to that effect. At oral argument, the plaintiffs

insisted that they are under no obligation to make such an allegation. See Oral Argument Recording at 15:35-48.

The plaintiffs are wrong. "[I]t is the burden of the party who seeks the exercise of jurisdiction in his favor clearly to allege facts demonstrating that he is a proper party to invoke judicial resolution of the dispute." FW/PBS, Inc. v. City of Dallas, 493 U.S. 215, 231 (1990) (internal quotations and citations omitted). Thus, the plaintiffs "must 'allege...facts essential to show jurisdiction. If [they] fai[l] to make the necessary allegations, [they have] no standing.'" Id. (quoting McNutt v. Gen. Motors Acceptance Corp., 298 U.S. 178, 189 (1936)) (alterations and omissions in original). Plaintiffs have failed to make the necessary allegation here, and they therefore lack standing to raise this challenge.

IV

For the foregoing reasons, the judgment of the district court is

Affirmed.

Appendix 2 – District Court Opinion

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

)

THOMAS REMPFER, *et al.*,

Plaintiffs,

v.) Civil Action No. 06-2131 (RMC)

)

ANDREW C. VON ESCHENBACH,

Commissioner Food and Drug

Administration, *et al.*,

Defendants.

MEMORANDUM OPINION

Plaintiffs[1] are military personnel subject to orders to take Anthrax Vaccine Adsorbed ("AVA"), the only vaccine in the U.S. licensed as a prophylactic against anthrax. They brought this suit against the Food and Drug Administration (FDA), the Department of Health and Human Services (HHS), and the Department of Defense (DoD)[2]

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[1] Plaintiffs are: Thomas Rempfer, Joshua Cohen, Gareth Harris, Kevin Ferrara, Shameka Edwards, Eric Gearhart, Michael Palmer, and James Hailstone.

[2] The complaint names, in their official capacities, the following: Andrew Von Eschenbach, Commissioner, FDA; Mike Leavitt, Secretary, HHS; and Robert Gates, Secretary, DoD. The FDA is an agent of HHS.

(collectively "Defendants"), challenging (1) the FDA's Final Order, *see* 70 Fed. Reg. 75,180 (Dec. 19, 2005), which determined that AVA is safe and effective and not misbranded,[3] and (2) the DoD's decision to reinstate mandatory AVA inoculations. Plaintiffs do not contend that AVA is unsafe or misbranded; instead they allege that there is insufficient evidence that AVA is effective to prevent anthrax infection acquired through inhalation. Defendants move to dismiss. Upon reviewing the pleadings and the administrative record and in deference to the FDA's evaluation of scientific data, Defendants' motion will be granted.

I. BACKGROUND

Anthrax is a bacterial disease caused by spores of Bacillus anthracis. Anthrax spores can cause infection through three routes: skin contact (cutaneous), ingestion, and inhalation. Without antibiotic treatment, inhalation anthrax has the

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[3] Plaintiffs' counsel here instituted prior litigation, *Doe v. Rumsfeld*, Civ. No. 03-707 (D.D.C.), related to AVA. In that suit, six John and Jane Doe plaintiffs sought to challenge the DoD's immunization program. The court enjoined DoD from inoculating service members, finding that the vaccine was not properly licensed since the FDA had not made a final decision regarding the investigational status of AVA. *Doe v. Rumsfeld*, 297 F. Supp. 2d 119, 131 (D.D.C. 2003). Soon after, the FDA issued a final order classifying AVA as safe and effective; as a result the injunction was stayed. *Doe v. Rumsfeld*, 297 F. Supp. 2d 200, 201 (D.D.C. 2004). The Doe plaintiffs then amended their complaint to challenge the FDA's final order. The Court, on cross motions for summary judgment, then determined that the FDA had issued the final order without proper notice and comment. The FDA withdrew the final order and proceeded with notice and comment. The FDA then issued a new Final Order, 70 Fed. Reg. 75,180, the one at issue here.

highest fatality rate — estimated to be 45% to 90%. A.R. at 639 (04 AR, Vol. 3).[4] Cutaneous anthrax has an estimated 20% fatality rate, and gastrointestinal anthrax has an estimated fatality rate of 25% to 60%. *Id.* at 638-39. In the U.S., there were eighteen cases of inhalations anthrax from 1900 to October 2001,[5] mostly occurring in textile mill workers. *Id.* at 639. Sixteen of those cases were fatal. Then, from October 4, 2001 to December 5, 2001, there were eleven cases of inhalation anthrax, five of which were fatal. *Id.* The 2001 cases were all linked to intentional dissemination. *Id.* Regardless of the route of exposure, anthrax is toxic to the body in the same way. The "virulence components" of anthrax include an anitphagocytic capsule and three proteins: protective antigen, lethal factor, and edema factor. The combination of protective antigen with lethal factor causes the formation of cytotoxic lethal toxin, and the combination of protective antigen with edema factor results in edema toxin. *Id.*

In 1965, DoD contracted with the Michigan Department of Public Health ("MDPH") to produce an anthrax vaccine. A.R. 3647-52 (04 AR, Vol. 13). Before the MDPH contact, DoD had contracted with Merck Sharpe & Dohme to produce an anthrax vaccine and prior to that the Army had produced a vaccine (the "original vaccine" or the "DoD vaccine").

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[4] "A.R." refers to the Administrative Record consisting of 4209 pages originally filed in 2004, see Doe v. Rumsfeld, Civ. No. 03-707 (D.D.C.), plus an additional 20,000 pages. The record first filed in 2004 has been refiled here in 15 volumes on a single CD; these documents are secondarily cited as "(04 AR, Vol. ___)". The additional 20,000 pages were filed here in 3 volumes on 3 CDs.

[5] The last case reported in this period occurred in 1976.

In 1966, the Center for Disease Control ("CDC") filed with the National Institute for Health ("NIH") a "Notice of Claimed Investigational Exemption" for the anthrax vaccine. Under this investigational new drug application, the CDC began an "open label study" to collect safety data on the MDPH vaccine; the study continued from year to year and the CDC provided annual progress reports to the NIH. The next year, MDPH filed a product license application with the NIH for the vaccine it was producing for DoD. During the licensing process, the MDPH vaccine was named AVA.

The NIH licensed AVA in 1970.[6] The NIH-approved package insert recommended AVA immunization for individuals with a risk of exposure to anthrax, those who come into contact with animal hides, bonemeal, and fur, especially goat hair. A.R. 3291 (04 AR, Vol. 12). The 7 059 labeling did not recommend immunization be limited to any particular route of exposure. A.R. 3291-92 (04 AR, Vol. 12). AVA was licensed to be given in a six dose regimen: three inoculations, each two weeks apart, and then three more given at six, twelve, and eighteen month intervals thereafter.

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[6] The committee from the NIH that recommended g 6 ranting the license application based its recommendation on the following: the CDC safety data, potency data from lab tests using AVA in guinea pigs, and additional standards relating to production and potency testing. While the committee noted that MDPH's vaccine had not been used in a controlled field trial, the original vaccine was used in a controlled study. Because the original vaccine and the MDPH vaccine were comparable, the FDA determined that the controlled study could be relied upon for proof of AVA's effectiveness. See text infra regarding Count III of the First Amended Complaint.

In 1973, the FDA announced a safety and effectiveness review for various vaccines, including AVA, and solicited data and information. 38 Fed. Reg. 5,358 (Feb. 28, 1973). The Panel that conducted the review issued a report in 1980. *See* A.R. 0001-0600 (04 AR, Vol. 1-2). In 1985, the FDA published the Panel's report and a proposed order relating to matters in the report. *See* 50 Fed. Reg. 51,002, (Dec. 13, 2005). As to AVA, the FDA agreed with the Panel's recommended that AVA be categorized as safe, effective, and not misbranded. 70 Fed. Reg. at 75,182; *see* 50 Fed. Reg. at 51,059.[7]

To determine whether AVA was effective, the Panel considered: (1) a controlled human field study conducted by Drs. Brachman, Gold, Plotkin, Fekety, Werrin, and Ingraham in the 1950s (the "Brachman Study"), *see* A.R. 3732-3745 (04 AR, Vol. 13), and (2) surveillance data collected by the CDC. *See* 50 Fed. Reg. at 51,058. The Brachman Study involved 1,249 workers in four textile mills that processed raw imported goat hair, a group at risk for anthrax infection.[8] *See* AR 3732-33 (04 AR, Vol. 13). The

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[7] There is a two-stage process for reviewing biological products licensed prior to July 1, 1972, such as AVA. See 21 C.F.R. § 601.25. First, the FDA Commissioner appoints a Panel of experts to review the safety, effectiveness, and labeling of the biological product at issue and to produce an advisory report. Id. § 601.25(a) & (e). Second, the Commissioner publishes the report and a proposed order in the Federal Register and solicits comments. Id. § 601.25(f). After reviewing the comments, the FDA publishes a final order, which constitutes final agency action from which appeal may lie to the courts. Id. § 601.25(g) & (i).

[8] In order to conduct a study of the effectiveness of the vaccine, the study required a "well defined, exposed, susceptible population among whom cases of anthrax were reported with

workers were divided into three groups: one received the anthrax vaccine; one received a placebo; and one was simply monitored for anthrax infection. *Id.* at 3732; 50 Fed. Reg. at 51,058. There were 26 cases of anthrax during the study period, five of which were individuals infected through inhalation. *See* AR 3734 (04 AR, Vol. 13); *id.* at 3736 (Table 4). None of the individuals with inhalation anthrax had taken the vaccine, two were in the placebo group, and three were in the observation group. The remaining twenty-one infected workers contracted cutaneous anthrax. Of those, three had taken the vaccine (although two had not been fully inoculated), fifteen were in the placebo group, and three were in the observation group. *Id.* Based on these facts, the Brachman Study concluded the effectiveness of the vaccine at 92.5%, comparing the vaccine group with the placebo group and combining the inhalation and cutaneous cases. *Id.* at 3737. The rate of effectiveness did not include data from the group that was simply monitored. *Id.*; A.R. 1381 at n.9 (04 AR, Vol. 6).

Although the Panel relied on the Brachman Study, the Panel found that the study demonstrated effectiveness only against cutaneous anthrax because the inhalation cases "occurred too infrequently to assess the protective effect of [the] vaccine against this form of the disease." Fed. Reg. at 51,058. "Anthrax vaccine poses no serious special problems other than the fact that its efficacy against inhalation anthrax is not well documented. This

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some regularity." See A.R. 3732 (04 AR, Vol. 13). This type of population could only be found in the U.S. in certain types of textile mills. Id. When the Panel submitted its report in 1980, this type of industry was "vanishing, precluding any further clinical studies." 50 Fed. Reg. at 51,058.

question is not amenable to study due to the low incidence and sporadic occurrence of the disease." *Id.* Even so, the Panel found the vaccine to be safe and effective for the limited circumstances for which it is employed. *Id.* Further, the Panel did not recommend any change in the "recommendations for use" section of the AVA label, which recommended AVA for immunization against anthrax, without any specification regarding route of exposure.[9]

In addition to the Brachman Study, the Panel relied on the CDC surveillance data as evidence of effectiveness as follows:

> [The data] were summarized for the period between 1962 to 1974. Twenty-seven cases were identified. Three cases were not mill employees, but worked in or near mills; none of these cases were vaccinated. Twenty-four cases were mill employees; three were partially immunized (one with 1 dose, two with 2 doses); the remainder (89 percent) being unvaccinated. Therefore, no cases have occurred in fully vaccinated subjects while the risk of infection has continued. These observations lend further support to the effectiveness of this product.

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[9] In the Final Order, discussed infra, the FDA found that the Panel's conclusion that the Brachman study demonstrated effectiveness only against cutaneous anthrax due to the low incidence of inhalation cases was in error, and that in fact the Brachman Study calculated the vaccine's effectiveness against cutaneous and inhalation anthrax. See A.R. 3736 (04 AR, Vol. 13 (Table 4); id. at 3740-41 (Table 8).

Id. Thus, based on the CDC surveillance data and the Brachman Study, the Panel found "substantial evidence of safety and effectiveness for this product [AVA]." *Id.* at 51,059.

In March of 1998, DoD implemented the Anthrax Vaccine Immunization Program to protect service personnel at risk of contracting anthrax. Congress then directed DoD to contract with the National Research Council to study the safety and effectiveness of AVA. A.R. 3324 (04 AR, Vol. 12). As a result, the Institute of Medicine's Committee to Assess the Safety and Efficacy of the Anthrax Vaccine (the "IOM Committee") conducted an independent study over the course of two years. A.R. 3303-583 (04 AR, Vol. 12). The IOM Committee[10] sought, reviewed, and weighed "[a]ll available data." *Id.* at 3309. The Committee issued a report finding, "As indicated by evidence from studies in both humans and animals, the committee concluded that AVA, as licensed, is an effective vaccine to protect humans against anthrax, including inhalational anthrax," and it is "reasonably safe." *Id.* at 3323.

In its 2005 Final Order, the FDA agreed with the report of the IOM Committee and its finding that AVA was effective. 70 Fed. Reg. at 75,183. The FDA disagreed with the Panel's 1985 opinion that the Brachman Study did not have sufficient data to

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[10] The IOM Committee was composed of ten experts from respected institutions such as Harvard University and the University of Pennsylvania School of Medicine. Their collective knowledge included expertise in microbiology, epidemiology, biostatistics, immunology, and health surveillance, as well as vaccine research, development, manufacture, evaluation, and post-marketing surveillance of adverse events. A.R. 3325 (04 AR, Vol. 12).

demonstrate the effectiveness of AVA against inhalation anthrax. The FDA explained:

> We do not agree with the Panel's statement that the protection [provided by AVA] was limited to cutaneous anthrax cases. The Brachman [S]tudy's comparison between anthrax cases in the placebo and vaccine groups included both inhalation and cutaneous anthrax cases. Accordingly, the calculated effectiveness of the vaccine to prevent both types of anthrax disease combined was 92.5 percent (lower 95 percent confidence interval = 65 percent) as described in the Brachman, *et al.* report.

Id. See also A.R. 3736 (04 AR, Vol. 13 (Table 4)); *id.* at 3740-41 (Table 8). The FDA noted that the CDC surveillance data supported the Brachman Study's findings regarding the effectiveness of AVA.[11]

The FDA received numerous comments relating to its Order. Comments supportive of AVA licensure included a submission by a researcher who discussed in detail "how the pathology of cutaneous and inhalation anthrax at the cellular level is fundamentally the same, i.e., dependent on the actions of anthrax toxin, such that cytotoxic activities are blocked by antibodies produced in response to AVA in the same manner despite the route of

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[11] The FDA also agreed with the Panel that the safety of AVA was demonstrated by the CDC open label safety study (described supra) that was initiated in 1966. 70 Fed. Reg. at 75,183 & 75,188. The CDC open label safety study should not be confused with the CDC surveillance data which corroborated the Brachman Study's findings regarding AVA's effectiveness.

exposure." 70 Fed. Reg. at 75,185. Comments against licensure included the same objections that Plaintiffs raise here. The FDA concluded, "After review of the comments and finding no additional scientific evidence to alter the proposed categorization, FDA accepts the Panel's recommendation . . . and determines AVA to be safe and effective and not misbranded." *Id.* at 75,182.

Counts I, II, and III of the First Amended Complaint challenge the FDA's Final Order. Plaintiffs seek temporary and permanent injunctive relief from DoD's anthrax vaccination program, alleging that the FDA's finding that AVA was effective against inhalation anthrax was arbitrary and capricious in violation of the Administrative Procedure Act ("APA"), 5 U.S.C. §§ 701 *et seq.* In Count IV, Plaintiffs seek a declaratory judgment that AVA is being administered in violation of 10 U.S.C. § 1107. Defendants seek dismissal of Counts I, II, and III based on failure to state a claim and on Count IV based on lack subject matter jurisdiction due to lack of standing. Plaintiffs oppose.

II. STANDARD OF REVIEW

A. Failure to State a Claim

A motion to dismiss pursuant to Federal Rule of Civil Procedure 12(b)(6) challenges the adequacy of a complaint on its face, testing whether a plaintiff has properly stated a claim. Although a complaint "does not need detailed factual allegations, a plaintiff's obligation to provide the 'grounds' of his 'entitle[ment] to relief' requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do." *Bell Atl. Corp. v. Twombly*, 127 S. Ct. 1955, 1964-65 (2007)

(internal citations omitted). The court must treat the complaint's factual allegations — including mixed questions of law and fact — as true, drawing all reasonable inferences in the plaintiff's favor, *Macharia v. United States*, 334 F.3d 61, 64, 67 (D.C. Cir. 2003); *Holy Land Found. for Relief & Dev. v. Ashcroft*, 333 F.3d 156, 165 (D.C. Cir. 2003), and the facts alleged "must be enough to raise a right to relief above the speculative level," *Twombly*, 127 S. Ct. at 1965. But the court need not accept as true inferences unsupported by facts set out in the complaint or legal conclusions cast as factual allegations. *Browning v. Clinton*, 292 F.3d 235, 242 (D.C. Cir. 2002).

B. Lack of Subject Matter Jurisdiction

Federal courts are courts of limited jurisdiction and the law presumes that "a cause lies outside this limited jurisdiction." *Kokkonen v. Guardian Life Ins. Co. of Am.*, 511 U.S. 375, 377 (1994). Because subject matter jurisdiction is an Article III as well as a statutory requirement, "no action of the parties can confer subject-matter jurisdiction upon a federal court." *Akinseye v. District of Columbia*, 339 F.3d 970, 971 (D.C. Cir. 2003). On a motion to dismiss for lack of subject-matter jurisdiction pursuant to Rule 12(b)(1), the plaintiff bears the burden of establishing that the court has subject matter jurisdiction. *Evans v. B.F. Perkins Co.*, 166 F.3d 642, 647 (4th Cir. 1999); *see also McNutt v. Gen. Motors Acceptance Corp.*, 298 U.S. 178, 182-83 (1936)). Because subject matter jurisdiction focuses on the court's power to hear the claim, however, the court must give the plaintiff's factual allegations closer scrutiny when resolving a Rule 12(b)(1) motion than would be required for a

Rule 12(b)(6) motion for failure to state a claim. *Macharia v. United States*, 334 F.3d 61, 64, 69 (D.C. Cir. 2003). To determine whether it has jurisdiction over the claim, the court may consider materials outside the pleadings. *Herbert v. Nat'l Acad. of Scis.*, 974 F.2d 192, 197 (D.C. Cir. 1992).

C. APA Review

The APA requires a reviewing court to set aside an agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A); *Tourus Records, Inc. v. Drug Enforcement Admin.*, 259 F.3d 731, 736 (D.C. Cir. 2001). In making this inquiry, the reviewing court "must consider whether the [agency's] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Marsh v. Oregon Natural Res. Council*, 490 U.S. 360, 378 (1989) (internal quotation marks and citation omitted). At a minimum, the agency must have considered relevant data and articulated an explanation establishing a "rational connection between the facts found and the choice made." *Bowen v. Am. Hosp. Ass'n*, 476 U.S. 610, 626 (1986); *see also Pub. Citizen, Inc. v. Fed. Aviation Admin.*, 988 F.2d 186, 197 (D.C. Cir. 1993) ("The requirement that agency action not be arbitrary or capricious includes a requirement that the agency adequately explain its result."). An agency action usually is arbitrary or capricious if

> the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs

> counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.

Motor Vehicle Mfrs. Ass'n of U.S. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983); *see also County of Los Angeles v. Shalala*, 192 F.3d 1005, 1021 (D.C. Cir. 1999) ("Where the agency has failed to provide a reasoned explanation, or where the record belies the agency's conclusion, [the court] must undo its action.").

As the Supreme Court has explained, "the scope of review under the 'arbitrary and capricious' standard is narrow and a court is not to substitute its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 43; *see Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996) ("we might not have chosen the FDA's course had it been ours to chart...[b]ut that is hardly the point."). Rather, the agency action under review is "entitled to a presumption of regularity" and the court must consider only whether the agency decision was based on relevant factors and whether there has been a clear error of judgment. *Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 415 (1971), *abrogated on other grounds by Califano v. Sanders*, 430 U.S. 99 (1977).

In cases involving scientific or technical decisions within the agency's area of expertise, the agency is entitled to a "high level of deference." *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998). When confronted with subject matter characterized by scientific and technological uncertainty, courts " must proceed with particular

caution, avoiding all temptation to direct the agency in a choice between rational alternatives." *Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166, 177 (D.D.C. 2000). Judges are not "scientists independently capable of assessing the validity of the agency's determination"; instead of making an independent assessment, courts must hold the agency to the standards of rationality required by the APA. *Serono Labs.*, 158 F.3d at 1327; *accord Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) ("we review scientific judgments of the agency [the EPA] not as the chemist, biologist, or statistician that we are qualified neither by training nor experience to be, but as a reviewing court exercising our narrowly defined duty of holding agencies to certain minimal standards of rationality."). The determination of whether a drug is effective "necessarily implicates complex chemical and pharmacological considerations." *Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 654 (1973). The FDA's judgments regarding efficacy fall within the FDA's expertise and thus such judgments merit deference from the courts. *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 220 (D.D.C. 1996). Further, the "FDA's policies and its interpretation of its own regulations will be paid special deference because of the breadth of Congress' delegation of authority to FDA and because of FDA's scientific expertise." *Berlex Labs., Inc. v. FDA*, 942 F. Supp. 19, 25 (D.D.C. 1996).

In reviewing an administration action such as the FDA's Final Order at issue here, the role of the district court is to "sit as an appellate tribunal" and review the case as a matter of law. *Marshall County Health Care Auth. v. Shalala*, 988 F.2d 1221, 1226

(D.C. Cir. 1993). Such review is limited to the administrative record, and "not some new record made initially in the reviewing court." *Camp v. Pitts*, 411 U.S. 138, 142 (1973); *accord Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166, 177 (D.D.C. 2000). Thus, here the Court reviews the pleadings and the administrative record; the Court may not review any new materials submitted by either party.

III. ANALYSIS

Counts I through III each challenge the FDA's finding that AVA is effective. The standards for the FDA and its Panels to apply in evaluating safety, effectiveness, and labeling are set forth in 21 C.F.R. § 601.25(d). Effectiveness is defined as follows:

> Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biologic product, when used under adequate directions, for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment, or prevention of disease in man.

21 C.F.R. § 601.25(d)(2). Proof of effectiveness "shall consist of controlled clinical investigations" as defined in 21 C.F.R. § 314.126, unless this requirement is waived or alternate methods are adequate to substantiate effectiveness. *Id.* Such controlled clinical investigations "may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing." *Id.*

A. Counts I and II

Plaintiffs' allegations in Counts I and II of the First Amended Complaint are overlapping. In Count I, Plaintiffs assert that the FDA relied on flawed scientific studies, the Brachman Study and the CDC safety surveillance data, to find that AVA was effective. First Am. Compl. ¶¶ 69-75. In Count II, Plaintiffs assert that there were too few incidents of inhalation anthrax in the Brachman Study to substantiate the vaccine's effectiveness.[12] *Id.* ¶¶ 90-92.

First, Plaintiffs allege that the FDA's reliance on the Brachman Study was improper because the study was not "well-controlled" as required by 21 C.F.R. § 601.25(d)(2). The FDA, in its scientific judgment, has found that the Brachman Study was well-controlled. *See* 70 Fed. Reg. at 75,182. This judgment is supported by the record. The Brachman Study was a field study that compared the results in an inoculated group against the results in a placebo control group, and thus by its very definition was a controlled study. AR 3734 (04 AR, Vol. 13); *id.* at 3736 (Table 4). Plaintiffs argue that in 1969 when the NIH reviewed the effectiveness of AVA (the MDPH vaccine), the NIH noted that the studies "did

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[12] In Count II, Plaintiffs also assert that at the time AVA was licensed in 1970 under the Public Health Service Act ("PHSA"), 42 U.S.C. §§ 201 et seq., it was found to be "potent" as required by the PHSA and it was not found to be "effective" as was required starting in 1972 under the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301 et seq. The fact that in 1970 there was no finding of effectiveness is not relevant because in 2005 the FDA in its Final Order did find that AVA is effective. See 70 Fed. Reg. 75,180. It is this finding of effectiveness that Plaintiffs challenge in this lawsuit.

not provide control data whereby the effectiveness of the vaccine could be evaluated." A.R. 3629-30 (04 AR, Vol. 13). In fact, the NIH did not refer to the Brachman Study at all, as the Brachman Study used the earlier version of the vaccine (the DoD vaccine), not the MDPH vaccine that the NIH was reviewing at the time.[13] The NIH documents that Plaintiffs cite discuss data generated from uncontrolled studies of the MDPH vaccine. The NIH was referring to the "Talladega" non-controlled epidemiological data and other uncontrolled studies listed at A.R. 3607-16 (04 AR, Vol. 13). *See* A.R. 3634 (04 AR, Vol. 13) ("The lack of cases of anthrax in an uncontrolled population of approximately 600 persons in the Talladega mill can hardly be accepted as scientific evidence for the efficacy of the vaccine."). In a 1969 letter from the CDC to the NIH, the CDC director indicated, "[t]here have been no controlled evaluation studies with the Michigan [MDPH] anthrax product as was done by Dr. Philip Brachman using the [original/DoD] vaccine." A.R. 1375 (04 AR, Vol. 6).

Second, Plaintiffs allege that the FDA should not have combined statistics regarding cutaneous anthrax cases with inhalation anthrax cases when it evaluated the Brachman Study data. They argue that "modern statistical analysis of Brachman data reveals that there is no statistical correlation between vaccination with AVA and inhalation anthrax protection." Pls.' Resp. at 15. Plaintiffs, in essence, argue that cutaneous and inhalation anthrax are different outcomes and must be tested

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[13] The FDA concluded in its Final Order that these versions of the vaccine in fact are comparable. See discussion of Count III, infra.

for separately. If inhalation anthrax had been tested separately in the Brachman Study, the numbers would not have been sufficient for a statistical analysis — the two cases in the placebo group compared to no cases in the vaccinated group were just too few to be statistically significant.

However, the FDA, again in its scientific expertise, determined that the contraction of the anthrax disease was the proper outcome to be tested, regardless of the route of exposure. The Brachman Study compared the incidence of anthrax in a control group with the incidence in an inoculated group and determined that the vaccine was 92.5% effective against anthrax, combining both cutaneous and inhalation anthrax cases. The FDA determined that this type of statistical analysis was appropriate because the vaccine counteracts the anthrax bacteria in the same manner, no matter how the anthrax was contracted. Regardless of the route of infection, the anthrax bacteria produces the same toxins and the vaccine acts against those toxins in the same manner. The FDA fully explained its analysis:

> The inclusion of both cutaneous and inhalation cases of anthrax in the analysis of the Brachman [S]tudy was appropriate because it was not possible to predict the route of exposure (cutaneous versus inhalation) that would occur within the environmental setting of the woolen mills. With regard to the known pathophysiology of anthrax, the signs and symptoms of disease arise due to the production of toxins by anthrax bacteria growing within the infected individual. The

> toxins produced by anthrax bacteria do not vary based on route of exposure. The antibodies produced in response to vaccination contribute to the protection of the vaccinated individual by neutralizing the activities of those toxins. Thus, AVA elicits an antibody response to disrupt the cytotoxic effects of toxins produced by anthrax bacteria, regardless of the route of infection.

70 Fed. Reg. at 75,187.

Third, Plaintiffs contend that the fact that inhalation anthrax is more deadly than cutaneous anthrax shows that the bacteria acts differently depending on the route of infection. Pls.' Resp. at 7. Plaintiffs cite no support for this proposition. FDA has explained that inhalation anthrax has a higher fatality rate than cutaneous anthrax because it generally results in a systemic infection whereas cutaneous anthrax generally results in a localized infection. *See, e.g.*, A.R. 3363-64 (04 AR, Vo. 12).

Fourth, Plaintiffs contend that the FDA improperly relied on (1) the CDC surveillance data and (2) animal studies. In making a finding of effectiveness, the FDA can rely on a controlled clinical study such as the Brachman Study, and the controlled clinical study may be "corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing." 21 C.F.R. § 601.25(d)(2). "Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered." *Id.* Under this regulation, the FDA

considered the CDC surveillance data as "reports of significant human experience during marketing." Similarly, the FDA found that studies in human and animal models cited in the IOM report supported the conclusion that AVA was effective against anthrax regardless of the route of exposure. 70 Fed. Reg. at 75,183. For example, the IOM Committee noted that the pathology of anthrax in macaques "best mimics that seen in humans after inhalation exposure," A.R. 3385 (04 AR, Vol. 12), and concluded that AVA is effective in protecting macaques from inhalation exposure to the strains of anthrax tested. *Id.* at 3389. Pursuant to section 601.25(d)(2), the FCA cited the IOM's conclusions from animal studies to corroborate the Brachman Study. The FDA's interpretation of its own regulation, as permitting corroboration by the CDC surveillance data and animal studies, was not plainly erroneous and must be afforded deference. *Berlex Labs.*, 942 F. Supp. at 25 (the FDA's interpretation of its own regulations should be paid special deference because of its scientific expertise). Accordingly, the FDA's reliance on the CDC surveillance data and animal studies as corroborating evidence was proper.

B. Count III

In Count III, Plaintiffs assert that the current AVA vaccine, manufactured by the MDPH, was never tested and thus the FDA cannot attest to its efficacy; the Brachman Study tested the original DoD vaccine manufactured by the Army. The FDA may base its approval on studies done with a prior version of a vaccine if it finds that the two versions are comparable in terms of safety and effectiveness. Products may be comparable, so long as the manufacturers have shared critical manufacturing

process information. A.R. 1399-1406 (04 AR, Vol. 6) (FDA comparability policy).

Here, the FDA found that AVA and the original vaccine were comparable under "FDA's long-standing approach to comparability," which permits a manufacturer to make manufacturing changes in producing a product "without performing additional clinical studies to demonstrate the safety and effectiveness of the similar product if data regarding the manufacturing changes support the conclusion that the versions are comparable." 70 Fed. Reg. at 74,184. Applying this approach and after reviewing the development of AVA, the FDA found AVA and the original vaccine were comparable. *Id.* "[C]linical data comparing the safety and immunogenicity of [AVA] vaccine with [the original] vaccine . . . reveal[ed] that the serological responses to [AVA] and [the original] vaccine were similar with respect to peak antibody response and seropositivity." *Id.* The FDA concluded that the two versions of the vaccine "are comparable in their ability to protect test animals . . . and their ability to elicit similar immune responses in humans" and thus the data from test studies of the original vaccine could be used to approve AVA. *Id.*

Plaintiffs argue that the FDA may not compare AVA and the original vaccine because the comparability policy only applies to products made by a single manufacturer and AVA and the original vaccine were made by different manufacturers. First Am. Compl. ¶ 99. The FDA comparability policy does not state that it is limited to products made by a single manufacturer.

Further, Plaintiffs claim that the FDA simply "declared" AVA and the original vaccine to be comparable as part of this litigation, that the FDA did not make a legitimate finding of comparability. This claim is not borne out by the record. As quoted above, the FDA reviewed the development of the anthrax vaccine and examined the clinical data comparing the safety and immunogenicity of AVA and the original vaccine. *See* A.R. 3698-3705 (AR 04, Vol. 13) (clinical data). As the FDA noted in its Final Order, "after a manufacturing change, a manufacturer may use data gathered with a previous version of its product to support the effectiveness of a comparable version of the same product." 70 Fed. Reg. at 75,184; *see also* A.R. 1383-84 (04 AR, Vol. 6) (the FDA's 2002 statement that the DoD vaccine is comparable to the BioPort [aka AVA] vaccine). In sum, the FDA's determination of comparability, based on its review of scientific data, is supported by the record.

C. Count IV

In March of 1998, DoD implemented the Anthrax Vaccine Immunization Program ("AVIP") to protect service personnel at risk of contracting anthrax. Pursuant to this Program, DoD has inoculated active duty and reserve members of the armed forces against anthrax with AVA, via the recommended the six dose regimen: three inoculations, each two weeks apart, and then three more inoculations at six, twelve, and eighteen month intervals thereafter. *See* First Am. Compl. ¶¶ 10 & 25. In July of 2000, DoD suspended the AVIP due to a shortage of AVA. *Id.* ¶ 58. Thus, immunization was interrupted for those military personnel who had not completed the six dose regimen at the time the AVIP

was suspended. On October 16, 2006, DoD announced the resumption of the AVIP for military personnel and "emergency-essential" DoD civilians and contractors. *Id.* ¶ 48. Plaintiffs allege:

> As part of this suspension, DoD announced that members of the Armed Forces who had received at least one of the sequences of six vaccinations required by the AVA product license would be subject to a modified vaccination schedule that is inconsistent with the vaccination schedule required by the AVA license. Specifically, DoD announced that members who had received one or more vaccinations, but who had not completed the six shot sequence of vaccinations, would not be required to restart the inoculation sequence as long as they received a subsequent shot within two years of their last vaccination.

Id. ¶¶ 59; *see also id.* ¶ 61 & 63 (DoD requires individuals who had their doses deferred must continue with the next dose in the series when directed.) *Id.* ¶ 61.

Thus, Plaintiffs claim that some military personnel will be subject to mandatory immunization under a modified drug regimen schedule that was not approved by the FDA. Because DoD intends to follow a vaccination schedule (for personnel whose vaccine regimen was interrupted) which is inconsistent with AVA's FDA-approved inoculation schedule, in those cases AVA is a drug allegedly unapproved for its applied/intended use. *Id.* ¶ 107. Under 10 U.S.C. §

1107, drugs unapproved for their applied uses may not be given to members of the Armed Forces without their informed consent except in the case of a Presidential waiver. Plaintiffs allege that they have not consented to unapproved anthrax inoculation by the DoD. *Id.* ¶ 111.

Although Plaintiffs allege that for certain military personnel DoD approved a vaccination schedule inconsistent with product instructions, Plaintiffs have not alleged that they themselves have been, or imminently will be, subjected to such a vaccination schedule and thus they lack standing to bring this claim. To withstand a motion to dismiss for lack of standing, a plaintiff must allege facts "demonstrating that he is a proper party to invoke judicial resolution of the dispute." *FW/PBS, Inc. v. City of Dallas*, 493 U.S. 215, 231 (1990). The facts alleged "must be enough to raise a right to relief above the speculative level." *Twombly*, 127 S. Ct. at 1965. To assert standing, an Article III jurisdictional requirement, a plaintiff must allege: (1) an actual or imminent injury in fact; (2) fairly traceable to the challenged action of the defendant; (3) likely to be redressed by a favorable decision. *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560-61 (1992). Because Plaintiffs have not alleged that they have suffered, or imminently will suffer, an injury due to an off-label inoculation schedule, they lack standing to bring this claim and the Court lacks jurisdiction over it. Count IV will be dismissed.[14]

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[14] Although none of the Plaintiffs is a civilian, Plaintiffs assert that civilian DoD employees and DoD contractors should be covered by 10 U.S.C. § 1107. Pls.' Resp. at 22. Section 1107 expressly applies only to members of the armed forces. 10 U.S.C. § 1107 (this section applies when "the Secretary of

IV. CONCLUSION

For the reasons explained above, the Court will dismiss Counts I, II, and III, Plaintiffs' APA challenge to the FDA's Final Order. After examining the available scientific data and interpreting the data pursuant to its regulations, the FDA applied its expertise and found that AVA is effective for immunization against anthrax, whether the infection was acquired by inhalation or cutaneously. The FDA did not act arbitrarily or capriciously. It considered the relevant data and articulated an explanation establishing a "rational connection between the facts found and the choice made." *Bowen*, 476 U.S. at 626. The Court will not substitute its own judgment when the FDA made no clear error of judgment. *See Overton Park*, 401 U.S. at 415-16 (the court must consider only whether the agency decision was based on relevant factors and whether there has been a clear error of judgment). In addition, the Court will dismiss Count IV because Plaintiffs lack standing to make a claim of off-label use under 10 U.S.C. § 1107.

Accordingly, Defendants' motion to dismiss[15] will be granted. Counts I, II, and III will be dismissed for failure to state a claim, and Count IV will be dismissed for lack of standing. A

Defense requests or requires a member of the armed forces to receive an investigational new drug or a drug unapproved for its applied use"). Even if a civilian were a named plaintiff in this suit, no claim could be stated under section 1107 on behalf of a civilian.

[15] Defendants' motion to dismiss [15 Dkt. # 15] was dismissed without prejudice by Minute Entry Order on August 3, 2007. Defendants renewed their motion to dismiss without amendment by filing a notice of such renewal [Dkt. # 29] on September 17, 2007.

memorializing order accompanies this Memorandum Opinion.

Date: February 29, 2008

_____/s/_____

ROSEMARY M. COLLYER

United States District Judge

Appendix 3 – GAO Report: GAO-02-181T

United States General Accounting Office

Tuesday, October 23, 2001

ANTHRAX VACCINE:

Changes to the Manufacturing Process

Statement of Nancy Kingsbury, Ph.D.,

Managing Director, Applied Research and Methods

Mr. Chairman and Members of the Subcommittee:

We are pleased to be here today to contribute to your hearing on biological warfare defense vaccine programs. This topic is of considerable urgency today in light of the terrorist attacks of September 11 and the exposures to anthrax in recent weeks. Our testimony today is limited to the work we have done in response to your October 2000 request to review the changes to the manufacturing process for the anthrax vaccine that has been produced by the BioPort Corporation and its predecessor entities. As you know, BioPort is the sole facility in the U.S. currently capable of producing anthrax vaccine.

My testimony today will address the changes that occurred in the manufacturing process for anthrax vaccine since 1989, and the status of the approval of those changes by the Food and Drug Administration (FDA). It is, of course, FDA's responsibility to determine that the anthrax vaccine is safe and efficacious, and it is our understanding that FDA officials will be undertaking a review in the near future to determine if vaccine production

can be resumed. We appreciate the opportunity to provide information that may be relevant to that determination.

A brief summary of our scope and methodology is provided in appendix I. A list of related GAO products is presented in appendix II.

Background

The original anthrax vaccine was developed by George Wright and others in the 1950s and was first produced on a large scale by the pharmaceutical company Merck Sharp & Dohme (Merck).[1] A clinical study in 1962 evaluated the safety and effectiveness of the Merck vaccine in mill workers.[2] The results of this study formed the basis for subsequent licensure of the vaccine in 1970. The original license for the production of anthrax vaccine was issued to the Michigan Department of Public Health by the Division of Biologics of the National Institutes of Health.[3] In 1995, the facility changed its name to the Michigan Biologic Products Institute. In 1998, the facility was sold, and its name was changed to BioPort Corporation.

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[1] Merck Sharp and Dohme is currently known as Merck and Co., Inc.

[2] The most common occurrence of anthrax infection has been in industrial settings like wool mills where workers may be exposed to infected animal products.

[3] Prior to the establishment of FDA as the licensing authority for vaccines, the National Institutes of Health was responsible for licensing.

Today, FDA, through the Center for Biologics Evaluation and Research (CBER), licenses biological products (that is, biologics) and the facilities in which they are produced. The manufacturer is required to comply with current Good Manufacturing Practices (cGMP) regulations, which regulate personnel, buildings, equipment, production controls, records, and other aspects of the vaccine manufacturing process.[4]

When there is a major change in the manufacturing process—defined as a change determined by FDA to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of a product in relation to safety or effectiveness—the manufacturer must submit evidence to FDA demonstrating that the change does not have any such adverse effects. This requirement is particularly important for vaccines since the quality of biologics cannot be ensured solely from final tests on random samples. Instead, the quality of biologics can be determined only by a combination of strict control of the entire manufacturing process, in process tests, and end-product tests. When significant process changes are made, the onus is on the manufacturer to ensure that the quality of the product is maintained after such changes are introduced. Depending on the changes made, this may require trial studies (with animals or humans)

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[4] cGMP embodies a set of scientifically sound methods, practices, or principles that are implemented and documented during development and production to ensure consistent manufacture of safe, pure, and potent products. Such principles apply to the manufacturing process as well as to the facilities in which products are manufactured. (21 C.F.R., parts 600 through 680.)

to evaluate the impact of the new process, followed by comparison of pre and post-change lots before releasing the post-change lots for use.[5]

As our testimony today reports, in the case of the anthrax vaccine, the Michigan facility did not notify FDA of a number of changes made in the manufacturing process in the early 1990s and no specific studies were undertaken to confirm that vaccine quality was not affected. FDA inspectors did not inspect the Michigan facility's anthrax production room until 1993. According to FDA, access was not granted because its inspectors had not been vaccinated against anthrax. FDA inspectors were able to perform some aspects of inspection—for example, reviewing records—but not equipment and production.[6]

The inspections that FDA ultimately was able to conduct over time found a number of deficiencies, many of which were not corrected in a timely manner. For example, the deficiencies that FDA identified it its February 1998 inspection fell broadly

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[5] FDA guidance states that, if significant changes to the manufacturing or formulation of a vaccine are made after the original clinical trial, bridging studies may be used to demonstrate that immunogenicity and the occurrence of common adverse events have not been affected adversely by these changes. Anthony, B.F. and A. Sutton, "The Role of the Food and Drug Administration in Vaccine Testing and Licensure," *New Generation Vaccines*, New York, Marcel Dekker, Inc., Ch. 73, p. 1191.

[6] The purpose of FDA's inspection is to determine that the products are manufactured in compliance with cGMP as described in the license application. Manufacturers who fail to meet product standards or who make unreported or undocumented changes in manufacturing methods may have their license suspended or revoked.

into two categories: (1) those that, although serious, might affect only one or a limited number of batches that were produced when the deficiency was extant and (2) those of a generic nature that could compromise the safety and efficacy of any batch or all batches. Vaccine production was suspended after these findings, and BioPort has been attempting since then to bring the facility and manufacturing process into compliance. We understand from recent testimony by the Secretary of Health and Human Services that BioPort has recently submitted an application for an FDA inspection to approve its facility and manufacturing process.

Changes to the Fermenters and Filters in the 1990s and FDA's Approval of Those Changes

Beginning in 1990, the Michigan state-owned facility (the Michigan facility) that was later sold to BioPort changed both the fermenters and the filters it used in manufacturing the anthrax vaccine.[7] With regard to fermenters, it replaced the original glass fermenter with two 100-liter stainless steel fermenters in 1990, and installed two similar fermenters in 1993. With regard to filters, the facility changed from ceramic to nylon filters in 1990. After the 1990 change, the facility changed the types of filters two more times, in 1996 and 1997. According to Michigan facility officials, changing the filters reduced processing time for the production of a single lot of anthrax vaccine, while changing and adding additional fermentors increased its production

[7] A fermenter is used to grow the bacteria. A filter is one of the processing stages after the fermentation. The filter removes whole bacteria and other biochemical components.

volume. We were informed that both changes were made to increase production before the onset of the Gulf War.

Under FDA regulations, changes to a vaccine manufacturing process are to be reported to FDA and significant changes may require the manufacturer to submit a license application amendment.[8] In December 1990, FDA was notified of the replacement of the original glass fermenter with two 100-liter stainless steel fermenters. FDA approved that change in 1993. Although the Michigan facility installed two additional stainless steel fermenters in 1993, it did not notify the FDA about the additional fermenters at that time. Inspection records indicate that FDA was aware of the additional fermenters and encouraged the facility to submit a license amendment application for them in 1993[9] and again in 1995.[10] In January 1999, BioPort submitted a

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[8] Prior to 1997, FDA regulations required that "important" proposed changes in the vaccine manufacturing process be reported to FDA at least 30 days prior to implementation. Since 1997, FDA regulations have required that "major" changes be reported to FDA at least 30 days prior to implementation and that FDA approve such changes prior to distribution of vaccine made using them.

[9] The FDA inspection report (May 26, 1993) stated that "any changes to the manufacturing [process] that have the potential to affect the safety, purity, or potency of a biologic must be submitted and approved by CBER prior to implementation."

[10] In April 1995, Michigan facility officials told FDA that the additional fermenters installed in 1993 were similar, although not identical, to those installed in 1990 and approved in 1993. In response, FDA officials explained that "a different fermenter may cause change in the product, even if the fermenter is similar to the existing fermenter, and would most likely require

license amendment application with supporting documentation to FDA concerning the two additional fermenters. In May 2001, FDA approved these additional fermenters.

Because we could find no evidence in BioPort or FDA records that the filter changes had been reported to FDA, we contacted FDA officials in December 2000 to discuss the filter changes. They told us that they had not been notified and were not aware of changes to any filters used to produce anthrax vaccine. In February 2001, FDA wrote to BioPort, raising questions about the changes to the filters. In April 2001, BioPort submitted documentation, primarily in-process tests and lot release data, to FDA to demonstrate that the filter changes had not had a significant impact on vaccine quality. FDA reviewed and accepted the data and approved the filter changes in July 2001. Although the lot release data included lots produced immediately before and after the filter changes, the data submitted did not include the type of data that, according to FDA officials, would normally have been required if a license amendment application had been filed contemporaneously with the changes, that is, a direct biochemical analysis of vaccine samples from before and after the changes. FDA officials told us that such a direct comparison is not possible now, because appropriate pre-1990 vaccine samples no longer exist.

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agency approval." (FDA/CBER Conversation Record, Apr. 21, 1995.)

Studies Suggest Possible Changes to the Anthrax Vaccine After the 1990 Manufacturing Changes

Because it is not now possible to definitively resolve the question of whether the anthrax vaccine produced after the filter changes is the same as that produced before the changes (a demonstration that is normally required in a license amendment application), we have reviewed other studies to see if evidence suggests that the question may need to be further examined. We have found two types of such evidence.

First, in an unpublished study performed in 1990, the Department of Defense (DOD) found up to a hundredfold increase in the protective antigen levels in lots produced after the filter change that year.[11] (Anthrax toxin is composed of protective antigen, lethal factor, and edema factor. The individual toxin components are not toxic. A protective antigen and lethal factor combination produces lethality, and a combination of protective antigen and edema factor cause swelling.)

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[11] J.W. Ezell and T. Abshire, "In Vitro Analysis of Michigan Department of Public Health Human Anthrax Vaccine", U.S. Army Medical Research Institute of Infectious Diseases, Bacteriology Division, Fort Detrick, MD, Oct. 25, 1990. This unpublished study applied a then-new methodology to measure protective antigen that had not been separately validated at the time but is widely used today, and Dr. Ezell told us that the results should be interpreted cautiously as a result. We have had the study reviewed by two experts in anthrax vaccine issues who did not see any evident reasons to question the study methodology. We believe at best, however, it is an indicator that protective antigen levels may have changed after the filter changes. Since it cannot be replicated, it is the only evidence available on this point.

In a subsequent article published in 1994, DOD researchers, referencing the earlier study, hypothesized that the filter change altered the composition of the vaccine by increasing the level of protective antigen in the finished product.[12] According to the authors of this article, when DOD questioned the Michigan facility about this increase in 1990, the responsible Michigan facility official attributed it to the change in the filter from ceramic to nylon.

There are no studies to show what the effect of a significant increase in protective antigen may be on safety or efficacy of the vaccine. However, because the tests that could have demonstrated that the product was not changed in a material way in the context of a timely license amendment application were not done, and cannot now be done, there is potential merit in evaluating the findings of the 1990 DOD study further. We discussed the DOD study further with FDA officials on October 15, 2001, and they told us that they had not evaluated the study because they did not have it. At their request, we have provided the study to them.[13]

Second, we have reported several times in earlier work that, before 1990, anthrax vaccine was used by a small number of at-risk individuals (for

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[12] B.E. Ivens [sic, "Ivins"] and others, "Efficacy of a Standard Human Anthrax Vaccine Against Bacillus anthracis Spore Challenge in Guinea Pigs," *Vaccine*, vol. 12 (1994), pp. 872-874.

[13] Because we had earlier discussed this study with both DOD and BioPort, we had assumed that one or both of them had referred the information to FDA. We had also asked FDA about the study in December 2000 but they did not request a copy from us at that time.

example, wool mill workers), and FDA did not have any system to report adverse reactions associated with drugs and vaccines. Safety data, as reported in the product insert, were limited to the information from studies done in the 1960s, long before the fermenter and filter changes discussed here. Published and unpublished data on anthrax vaccine use during the Gulf War and since 1998 show a significantly greater incidence of both local and systemic adverse reactions compared with rates reported in the product insert. For example, the product insert says that the following should be expected: (1) 30 percent of recipients should experience a mild local reaction; (2) 4 percent should experience a moderate local reaction; and (3) 0.2 percent should experience systemic reactions characterized by malaise and lassitude with chills and fever reported in only a few cases. This indicates that some reaction should be experienced by a total of 34.2 percent of recipients. By comparison, in a survey we conducted in calendar year 2000, 85 percent of National Guard and reserve forces in our survey who were given the anthrax vaccine reported some reactions, with local reactions experienced by 76.2 percent of recipients and systemic reactions experienced by 23.8 percent. Chills and fever were reported by between 9 and 11 percent of our surveyed vaccine recipients.[14] These results are consistent with unpublished DOD studies and other published epidemiological work we are aware of.[15]

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[14] The full results of our survey will be reported in the near future.

[15] We reported on the results of several DOD studies in *Anthrax Vaccine: Safety and Efficacy Issues* (GAO/T-NSIAD-00-48, Oct. 12, 1999.) See also Lea Steele, "Prevalence and

Because there are no data to evaluate the effect of the filter change on the characteristics of the vaccine product, it is difficult to determine whether these greater levels of adverse reactions could be related to changes in the vaccine associated with the filter changes. Ceramic filters (used before 1990) absorb proteins more than nylon ones, and the change to nylon filters in 1990 could theoretically have resulted not only in more protective antigen coming through but also other proteins. The end-product and in-process tests that BioPort submitted to FDA in 2001 in support of the filter changes may lack the capability to evaluate this possibility. Additional biochemical tests would have been required. For example, a filter change could have allowed more edema factor to pass through. The Michigan facility did not routinely test for edema factor in the product. We note that, since 1997, United Kingdom (U.K.) regulations have required the anthrax vaccine produced by the U.K. Center for Applied Microbiology and Research to be tested for both protective antigen and edema factor.[16]

Observations

General public health vaccines are produced according to cGMP and are in constant, routine use worldwide. This use permits real-time monitoring of whether the vaccines are performing properly. In

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Patterns of Gulf War Illness in Kansas Veterans: Association of Symptoms with Characteristics of Person, Place, and Time of Military Service." *American Journal of Epidemiology*, Vol. 152, No. 10, 2000, pp. 992-1002.

[16] The Center for Applied Microbiology and Research is the manufacturer of the U.K.'s only licensed anthrax vaccine.

contrast, bio-defense vaccines have no such ongoing reality check because of the absence of natural disease and relatively limited use. Thus, only in emergency situations are bio-defense vaccines subjected to the evaluations that public health vaccines undergo all the time. Accordingly, the stringent application of cGMP by FDA in its approval of the resumption of vaccine manufacture at BioPort, as well as subsequent monitoring of the manufacturing process, is vital to ensure that vaccines produced are safe, pure, and of high quality.

In view of the increasing importance that will be given to the anthrax vaccine in the current environment and whether or not the anthrax vaccine is approved for production in the near future, it is important to ensure that studies continue to evaluate the vaccine's safety and efficacy, particularly with respect to the effect of higher levels of protective antigen and possibly other proteins. If FDA reinstates BioPort's license to manufacture and distribute vaccine, such studies would be strengthened by the implementation, by FDA or DOD, or both of an aggressive active surveillance program to ensure the early identification and analysis of adverse reactions.

Mr. Chairman, this concludes my statement. I will be happy to answer any questions you or Members of this Subcommittee may have.

Contacts and Acknowledgments

For further questions regarding this testimony, please contact Nancy Kingsbury, Ph.D., at (202) 512-2700. Other individuals making key contributions to this testimony include Sushil K.

Sharma, Ph.D., DrPH; Jack Melling, Ph.D.; George Bogart; and David Gootnick, M.D.

Appendix I: Scope and Methodology

To conduct our work, we reviewed documents provided to us by FDA, DOD, and the Michigan facility/BioPort Corporation pertaining to the anthrax vaccine. In addition, we reviewed published and unpublished scientific reports on anthrax vaccine and on the safety and efficacy of the vaccine. In addition, we interviewed officials of FDA, DOD, the Michigan facility/BioPort, and experts in anthrax vaccine in U.S. and the U.K.

Appendix II: Related GAO Products

Gulf War Illnesses: Questions About the Presence of Squalene Antibodies in Veterans Can Be Resolved (GAO/NSIAD-99-5, Mar. 29, 1999).

Medical Readiness: Safety and Efficacy of the Anthrax Vaccine (GAO/TNSIAD-99-148, Apr. 29, 1999).

Contract Management: Observations on DOD's Financial Relationship with the Anthrax Vaccine Manufacturer (GAO/T-NSIAD-99-214, June 30, 1999).

Medical Readiness: Issues Concerning the Anthrax Vaccine (GAO/TNSIAD-99-226, July 21, 1999).

Anthrax Vaccine: Safety and Efficacy Issues (GAO/T-NSIAD-00-48, Oct. 12, 1999).

Medical Readiness: DOD Faces Challenges in Implementing Its Anthrax Vaccine Immunization Program (GAO/-NSIAD-00-36, Oct. 1999).

Medical Readiness: DOD continues to Face Challenges in Implementing Its Anthrax Vaccine Immunization Program (GAO/T-NSIAD-00-157, Apr. 2000).

Gulf War Illnesses: Questions About the Presence of Squalene Antibodies in Veterans Can Be Resolved (GAO/NSIAD-99-5, March 29, 1999).

Appendix 4 – Doe v. Rumsfeld Amicus Curiae

Case No. 04-5440

IN THE UNITED STATES COURT OF APPEALS FOR THE DISTRICT OF COLUMBIA CIRCUIT

JOHN DOE #1, *et al.*, Plaintiffs-Appellees,

v.

DONALD H. RUMSFELD, Secretary of Defense, *et al.*, Defendants-Appellants.

On Appeal from the United States District Court
For the District of Columbia
In 03 -CV0707, Honorable Emmet G. Sullivan

AMICUS BRIEF FOR THE STATE OF CONNECTICUT IN SUPPORT OF AFFIRMANCE

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The Department of Defense Anthrax Vaccine Immunization Program: Unproven Force Protection.

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Congress, 2 Session, House Report 106-

556, April 3, 2000.....3, 15, 16

Pursuant to Rule 29 of the Federal Rules of Appellate Procedure ("FRAP"), Attorney General Richard Blumenthal submits this *Amicus Curiae*

Brief on behalf of the State of Connecticut to present a view of the law that may assist the Court in this proceeding. The interest of the State of Connecticut in this proceeding is substantial, in that members of Connecticut's Air National Guard have been removed from their positions because of their refusal to take the anthrax vaccine in the absence of a presidential waiver, discussed in detail below. This *amicus* brief is specifically authorized by D.C. Cir. R. 29(a) (a "State ... may file an amicus-curiae brief without the consent of the parties or leave of court").

BACKGROUND

Anthrax is a bacterial disease caused by Bacillus Anthracis. Three types of anthrax diseases exist: (a) Cutaneous Anthrax caused by contact with infected animals or contaminated animal products; (b) Gastrointestinal Anthrax caused by ingestion of contaminated meat; (c) Inhalation Anthrax caused by inhalation of anthrax spores. There are currently two types of anthrax vaccine adsorbed ("AVA") available for human use: (a) a live attenuated spore vaccine (formerly used in the

Soviet Union); and (b) a protective antigen vaccine, using filtrates of attenuated strains of anthrax bacillusm developed in the United States and the United Kingdom.

The first field trial of a human anthrax vaccine, known as the Brachman Study, was conducted on workers at four goat-hair processing mills in the 1950's. In 1965 a patent was granted to the U.S. Army for an anthrax antigen. An application for a license was submitted to the National Institute of Health ("NIH") in 1967 by the Michigan Department of Public Health ("MDPH"), which had at that time set up a facility to manufacture the vaccine. The application was made two years before there was any licensure requirement of proving safety and efficacy. Michigan Biologics Products Institute ("MBPI") obtained the license for the AVA from MDPH. In 1970 MBPI obtained approval to manufacture the AVA from the NIH's Bureau of Biologics. MBPI was purchased by Bioport Corporation ("Bioport") in 1998 and MBPI/Bioport is the sole producer of the anthrax vaccine in the United States today. MDPH's 1970 application for a license was approved by FDA's precursor, the Department of Health, Education and Welfare ("HEW"), without proof of efficacy or safety. This is the only valid product license for AVA, and remains in place today. This license was obtained for use only in limited agricultural, industrial, and veterinary settings (notably, tanneries) as a protection against cutaneous contact anthrax.

Recent developments in biological warfare have increased the risk that a hostile force may disseminate anthrax as a weapon against military or civilian populations. Until the Gulf War, the

vaccine had been used sparingly. "Despite having been licensed for almost 30 years, the vaccine had not been widely used prior to the Gulf War." (The Department of Defense Anthrax Vaccine Immunization Program: Unproven Force Protection. Fourth Report by the Committee on Government Reform, 106th Congress, 2nd Session, House Report 106-556, April 3, 2000, p. 34, "House Report") (see Appendix at A-1). On September 20, 1996, after thousands of troops had already been inoculated, MBPI applied to the FDA to approve the old vaccine for a new use: the prevention of inhalation anthrax. No approval was given. Despite the FDA's failure to approve the vaccine for inhalation anthrax, on December 15, 1997, May 18, 1998 and March 30, 1999, Secretary of Defense William Cohen issued directives requiring all U.S. military personnel to be vaccinated with AVA against inhalation anthrax.

The Secretary's vaccination plan was based on the prior allegedly successful completion of all testing and operational criteria. This testing did not include controlled drug trials on humans.

The FDA issued a proposed order in 1985 and public comment was invited. No further action was taken until December 2003, when the District

Court held that the vaccine was not proven effective or licensed for use against inhalation anthrax. The District Court issued a preliminary injunction against the mandatory vaccination of the troops without informed consent or a presidential waiver, on the ground that the proposed order in 1985 had never been finalized and the vaccine was consequently still an

Investigational New Drug ("IND") for purposes of 10 U.S.C. § 1107.

On January 5, 2004, days after the court's decision, the FDA concluded its 18-year review, concluding that the AVA was safe and effective for use against bacillus anthracis, regardless of the route of exposure, and published a final rule and order to that effect. The District Court then lifted the preliminary injunction on the basis that a final rule and order had been issued. The District Court allowed the case to continue as to the new decision by the FDA, which was the subject of further hearings by the District Court. On October 27, 2004 the District Court granted summary judgment in favor of the plaintiffs, vacating the FDA's order classifying AVA as safe and effective for use against inhalation anthrax. The court issued a military-wide permanent injunction against defendants, prohibiting the use of AVA absent informed consent or a presidential waiver pursuant to 10 U.S.C. § 1107.

On January 27, 2005, the Department of Health and Human Services ("HHS") authorized the emergency use of AVA for the prevention of inhalation anthrax for individuals deemed by the Department of Defense ("DoD") to be at a heightened risk of exposure. This emergency use authorization, issued pursuant to 21 U.S.C. § 360bbb-3, requires DoD to revise its Anthrax Vaccine Immunization program to give personnel the option to refuse vaccination without threat of penalty or retaliation.

ISSUES

Whether the military-wide preliminary injunction against Defendants, prohibiting the use of AVA absent informed consent or a Presidential waiver, was correct?

Whether the military-wide permanent injunction against Defendants, prohibiting the use of AVA absent informed consent or a Presidential waiver, was correct?

SUMMARY OF ARGUMENT

The many reasons why Judge Sullivan's decisions on both the preliminary and permanent injunctions should be affirmed have been set forth in the plaintiffs' brief and in this brief as well. However, fundamentally this is a very simple case.

Congress in enacting 10 U.S.C. § 1107 made it absolutely clear that service members are not to be subjected to investigational new drugs without either (a) their informed consent or (b) a presidential waiver of the informed consent requirement. DoD's order violated this statute.

Before the federal government decided to "cut corners" and violate the requirements of 10 U.S.C. § 1107, everyone agreed that there was insufficient data on the safety and efficacy of the anthrax vaccine with respect to inhalation anthrax. The FDA, the author of the study, the DoD, the CDC and the manufacturer all agreed and acted on the basis that the vaccine was an IND with respect to inhalation anthrax.

Thus, in 1985 a panel appointed by the FDA to review the safety and efficacy of all vaccines

stated in the Federal Register about the Anthrax vaccine, "No meaningful assessment of its value against inhalation anthrax is possible due to its low incidence." Even the author of the study the government is relying upon, Dr. Philip S. Brachman, has said in 1999, "No assessment of the effectiveness of the vaccine against inhalation anthrax could be made because there were too few cases."

In 1985 the Department of the Army issued a Request for Proposals to develop a vaccine against inhalation anthrax stating, "there is no vaccine in current use which will safely and effectively protect military personnel against exposure to this hazardous bacterial agent...."

Ten years later, in 1995, the Director of the Medical Chemical and Biological Defense Research Program of the Department of the Army wrote to the manufacturer of the vaccine once again recognizing that the vaccine needed further studies in order to expand the indication for its use to include protection from aerosol exposure. In 1996 the vaccine manufacturer itself filed an investigational new drug application with the FDA.

In 1998, the Deputy Director for Science and Public Health of the Centers for Disease Control and Prevention stated, in a letter reported by the American Public Health Association, "Although the current anthrax vaccine has been shown effective in preventing the cutaneous form of anthrax, CDC is neither aware of definitive data that demonstrates that vaccine's ability to protect against inhalation anthrax...."

In 1999, the FDA proposed changing the requirements for licensing investigational drugs intended to counter biowarfare hazards to only require animal studies, and such a rule was implemented in 2002 pursuant to statute. However, the FDA did not rely on or refer to this new rule in its rulemaking approving the anthrax vaccine in 2004, instead relying principally on an outdated human study of cutaneous rather than inhalation anthrax. At any rate, the available animal studies do not meet the standards set by the 2002 statute and rulemaking for animal-only IND approval.

In sum, the evidence is overwhelming that the vaccine is an IND in terms of inhalation anthrax and hence the requirements of 10 U.S.C. § 1107 apply. DoD's order that service members take the vaccine even in the absence of informed consent violates that statute.

We would hasten to note that no one is saying the vaccine cannot be used (as it is now under the terms of the injunction) as long as informed consent is obtained or even involuntarily if the president issued a waiver of the informed consent requirement in accordance with the statute.

ARGUMENT

I The anthrax vaccine has never been licensed for protection against inhalation anthrax because it has not been proved safe and effective for that use.

The FDA's underlying prerequisite for the approval of any vaccine or drug is that it be proved safe and effective for its intended use. The AVA as

currently formulated and manufactured has never been proved safe and effective for the purpose of protecting humans against infection following inhalation of anthrax spores. It is not licensed for this purpose. In 1972, amendments to the Food Drug and Cosmetic Act ("FDAC") required that drug effectiveness claims be supported by evidence consisting of adequate and well-controlled investigations, including clinical investigations. Before 1972, proof of safety and effectiveness was not required. Therefore, AVA's license by the Division of Biological Standards in 1970 was granted under old law and transferred to Bioport without any necessity that it meet current standards of proof of safety and effectiveness. Biologics, such as vaccines, were not subjected to formal efficacy review requirements when the AVA was licensed.

A clear process is laid out in 21 C.F.R. § 601.25 for reviewing biological products licensed prior to July 1, 1972. An advisory panel is appointed by the Commissioner of FDA ("Commissioner"). The panel first evaluates the safety and effectiveness of the previously licensed product. Second, it reviews the labeling of the product. Third, the panel submits a report as to what products are safe, effective, and not misbranded, and the Commissioner reviews the report, and then publishes the panel's report and a proposed order. Comments are submitted on the proposed order and the Commissioner then publishes a final order, which is the final agency action.

Licensing of drugs not licensed prior to July 1, 1972 by the FDA is a four step process outlined in 21 C.F.R. § 312 ("Section 312"). A drug goes through

phases of pre-clinical review, testing as an investigational new drug, a product license application procedure, and, finally, a post-licensure state.

An investigational new drug ("IND") is defined as a "new drug or biological drug that is used in a clinical investigation." 21 C.F.R. § 3 12.3(b). If a pharmaceutical company intends to conduct a clinical trial with an investigational new drug, it must submit an IND application to the FDA.

The clinical investigation of a previously untested drug is usually divided into three phases. Phase 1 studies are the closely monitored introduction of the investigational drug into humans. These studies are designed to determine side effects, metabolism, pharmacological action, and if possible, effectiveness. Phase 2 consists of controlled clinical trials to determine the effectiveness of the drug for the particular indication being studied. During Phase 3 studies, the number of subjects is expanded to several hundred or several thousand. These studies are performed to gather additional information about safety and effectiveness, after initial evidence of efficacy is obtained.

A drug that has reached the investigational phase of testing is at that point defined by the FDA as a "new drug". The term "new drug" includes previously licensed drugs, if the application is for a change in the purpose for which the drug will be used. *U.S. v. Articles of Drug Consisting of the Following: 5906 Boxes*, 745 F.2d 105 (1st Cir. 1984). Pursuant to these requirements, on September 21, 1996, MBPI filed an IND with the FDA

which identified three areas where the current license should be modified: a new purpose designation for "inhalation anthrax;" changing the "route of administration;" and changing the "vaccination schedule." IND Application (September 20, 1996). The significant changes in the proposed designation of the use for AVA and the vaccination schedule, as well as the route of administration, make AVA as it was being used by the military an unapproved "new" drug and an IND because its manufacturer initiated an application for a new use of an existing drug including a change in formula, dilution or repackaging.

The AVA was licensed in 1972, and its efficacy against cutaneous anthrax was addressed in 1985. However, the AVA's effectiveness in preventing inhalation anthrax has never been assessed in accordance with established IND procedures. The current IND process requires the submission of controlled studies proving that the drug is safe and effective for the proposed new use. No such studies have been conducted on the AVA. Furthermore, such controlled studies of a new drug pursuant to an IND application cannot be conducted on human subjects without their informed consent. IND's cannot be given to service members without informed consent or a presidential waiver. 10 U.S.C. § 1107.

II. There is no basis to assume that AVA's license encompasses use against inhalation anthrax.

On March 4, 1997, Stephen C. Joseph, M.D., M.P.H., the Assistant Secretary of Defense for Health Affairs wrote to Michael A. Friedman,

M.D., the lead Deputy Commissioner of Food and Drugs at the FDA, seeking permission to use the existing licensed AVA "to protect U.S. Forces against the threat of an Iraqi biological attack with anthrax." Notwithstanding that only eighteen months earlier the Department of the Army had written to MBPI recognizing that the existing license did not indicate the use of the anthrax vaccine against aerosol exposure, and that further studies were needed to accomplish that goal, Dr. Joseph stated in his letter that "while the package insert for this vaccine is nonspecific as to the route of exposure, DoD has long interpreted the scope of the license to include inhalation anthrax .... Please advise whether the FDA has any objection to our interpretation of the scope of the licensure for anthrax." On March 13, 1997, Michael A. Friedman, M.D., replied to Dr. Joseph, writing that there "is a paucity of data regarding the effectiveness of anthrax vaccine for prevention of inhalation anthrax." Dr. Friedman wrote that despite the lack of proof that the vaccine was effective against inhalation anthrax, its use for those purposes "is not inconsistent with the current label."

In his very short letter, with a stroke of the pen, Dr. Friedman wiped out ten years of DoD analysis and 25 years of FDA law designed to protect the safety and well being of the citizens of the United States. There was no justification, legal, scientific or otherwise for this action. For example, in a letter reported by the American Public Health Association, the Deputy Director for Science and Public Health of the Centers for Disease Control and Prevention, Claire Broome, stated on

December 14, 1998, that: "Although the current anthrax vaccine has been shown to be effective in preventing the cutaneous form of anthrax, CDC is neither aware of definitive data that demonstrates that vaccine's ability to protect against inhalation form of this disease in humans, nor are we aware of any data relative to the efficacy of this vaccine in humans exposed to genetically altered bacillus anthrax strains."

A scientific advisory panel submitted its report in 1980. The panel found that AVA is safe and effective for the limited use it was originally intended for, namely use by tannery and veterinary workers. The panel concluded that AVA is intended to be used for individuals with a high risk of cutaneous exposure. The panel never mentioned that AVA was intended to be used to prevent inhalation anthrax exposure. The proposed new use to vaccinate millions of troops against inhalational anthrax exposure places AVA squarely in the IND category.

III. There has not been sufficient testing conducted to show that AVA is safe and effective to use against inhalation anthrax.

The current vaccine's safety is in as much question as its efficacy. In a study, referred to as the Brachman Study, conducted in the 1950's at goat hair mills, volunteers receiving AVA were checked at 24 and 48 hours after vaccination. There was no active follow-up for side effects after that time. Based on this study, which is wholly inadequate by today's standards, the package insert listed a systemic side effect rate of 0.2%. However, two unpublished DoD

studies of the current vaccine cited by the Government Accounting Office (now, the Government Accountability Office) showed systemic side effect rates of 43% and 48%, over 200 times higher than reflected in the Brachman Study and the AVA package insert. This alone should have triggered an investigation and vaccine recall, according to Dr. Meryl Nass, a physician who has followed the anthrax vaccine closely. Dr. Nass has gone on to state, "there is not a single published study of the efficacy or safety of the current vaccine in humans. There are a number of unpublished studies which give short term systemic rates of 20% to 50% but no long term rates." (Prepared statement of Dr. Meryl Nass, NSVAIR, Anthrax hearing (II) p. 102). This lack of information about potential long-term side effects is a primary reason for the dissatisfaction with the program, and a compelling reason why the program should be voluntary. See House Report at 38 (Appendix at A-2).

The FDA amended the vaccine label and in January 2002 the new FDA- approved product insert listed many new adverse effects and a much higher rate of occurrence. Listed effects included deaths, birth defects, and a wide array of autoimmune disorders. The intention of this change was to warn the consumer of the possible side effects. However, military personnel being vaccinated typically do not see the package insert, and were required to submit to the vaccine or be court martialed.

The Advisory Panel's 1980 report considered both the Brachman Study and surveillance data collected and summarized by the CDC. The

Brachman Study purports to show the 1950's version of AVA to be 93% effective. However, at best, this study only shows that AVA is 93% effective against cutaneous anthrax, because inhalation anthrax occurs infrequently in the tanneries such as those involved in the Brachman Study. The CDC surveillance data similarly was collected in industrial settings with low rates of inhalational anthrax exposure. These studies illustrate that AVA is proven effective in preventing cutaneous anthrax, but as to inhalational anthrax, AVA has never been tested and it is not proved safe or effective.

On March 30, 2000, in response to a DoD request, the Institute of Medicine's Committee on Health Effects Associated With Exposure During the Gulf War provided the DoD with a letter entitled, "An Assessment of the Safety of the Anthrax Vaccine." The Institute, after examining the literature, was unable to conclude that the vaccine was free from long term health risks. "The Committee concluded that in the peer reviewed literature there is inadequate/insufficient evidence to determine whether an association does or does not exist between anthrax vaccination and long term health outcomes." According to the House Report (House Report at p. 41) (Appendix at A-3), "Studies have not been performed to evaluate the effects of AVA on carcinogenesis, mutagenesis or impairment of fertility."

Because the vaccine is still investigational, the military certainly may use AVA, but subject to the 10 U.S.C. § 1107 requirements of either informed consent, or a presidential waiver of the informed consent requirement. However, prior to Judge Emmet G. Sullivan's decision, service

members were not being asked for their informed consent. Instead and incredibly, refusal to take the vaccination was treated as insubordination with imprisonment, loss of pay or discharge from the military, contrary to 10 U.S.C. § 1107 and Executive Order 13139, which requires the DoD to obtain informed consent from each individual member of the armed forces before an IND can be administered.

The vaccine is not being administered according to the license.

Prior to the injunction, and presumably still, the AVA is not being administered according to the provisions of the existing license because the drug is administered subcutaneously rather than intramuscularly, as specified in the license. The pertinent regulation, 21 C.F.R. § 312, clearly provides that the method of administering a drug is an integral part of the Product License Application Process. Any change to the license-specified method of administration constitutes a new use of the AVA.

The new use of the AVA was not in accordance with its product labeling, and provides a separate and independent ground rendering the AVA investigational under FDA regulations, triggering the consent requirements and other requirements of 10 U.S.C. § 1107.

Since the anthrax vaccine has not been tested on humans there is no basis for concluding that it is safe and effective.

The FDA has established procedures that must be followed before a drug can be labeled safe and effective. An important component of the procedure is human testing. The FDA procedures

leading to a finding of "safe and effective" includes the following steps: (a) Studies are initiated in animals to define a safe and effective dose; (b) Results are submitted to the FDA, once accepted, human studies are allowed; (c) Human studies are designed to demonstrate safety and efficacy in the investigational product; (d) Two adequate, well controlled studies are necessary to demonstrate the efficacy of the product in humans.

21 U.S.C. § 355(d) was amended by the FDA Modernization Act of 1997 to allow under certain circumstances, "If the Secretary determines ... that data from one adequate and well-controlled clinical investigation and confirmatory evidence obtained prior to or after such investigation are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence...." Public Law 105-115 Sec. 115.

First, no one has asked the Secretary to make the determination that two adequate and well-controlled clinical investigations are not necessary. Second, the FDA itself makes clear that the Act "... does not lower the standards by which medical products are introduced into the market place." FDA Backgrounder, The FDA Modernization Act of 1997 (November 21, 1997) (Appendix at A-7). Also the FDA makes clear that in its view, "The act, however, does preserve the presumption that as a general rule, two adequate and well-controlled studies are needed to prove the product's safety and effectiveness." Id. (emphasis in original). Third, given the gross inadequacies of the Brachman study, in which there was insufficient data on inhalation anthrax to draw any conclusion about the vaccine's effectiveness with respect to

inhalation anthrax, the Secretary could not meet the statutory requirement. The Brachman study is not an "adequate and well-controlled" investigation with respect to inhalation anthrax. See 21 U.S.C. § 355(d).

In 1985 a panel appointed by FDA to review the safety and efficacy of all vaccines made the following observations about the current anthrax vaccine: "No meaningful assessment of its value against inhalation anthrax is possible due to its low incidence." FDA, "Biologic Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Proposed Rule," 50 Fed. Reg. 51059 (Dec. 13, 1985) (Appendix at A-8).

In 1994 and again in 1999, Dr. Philip S. Brachman, author of the 1962 Brachman study, and Col. (Dr.) Arthur Friedlander, the Army's chief anthrax researcher, coauthored the anthrax vaccine chapter in the medical text "Vaccines". They reiterated in both the 1994 edition and the 1999 edition: "No assessment of the effectiveness of the vaccine against inhalation anthrax could be made because there were too few cases." Plotkin and Mortimer, Vaccines (W.B. Saunders 2d ed., 1994); P.S.

Brachman and A.M. Friedlander, chapter 26, "Anthrax Vaccine" (p. 736). See also Plotkin and Orenstein, Vaccines, (W.B. Saunders 3d ed., 1999); P.S. Brachman and A.M. Friedlander, chapter 24, "Anthrax Vaccine" (p. 635).

Because exposing humans to a potentially lethal substance would be unethical and immoral, such testing has never been done on the AVA. Thus, the vaccine has never advanced beyond the

investigational stage. Absent human testing, there can be no claim by the DoD that the AVA is anything but an investigational drug. This result – that drugs that cannot be tested in humans cannot be administered without disclosure and consent (or a presidential waiver thereof) – is entirely appropriate and in keeping with the applicable laws and regulations. Patients have a right to know that a drug has not been tested in humans.

The very fact that BioPort (the vaccine's manufacturer) submitted an IND application for AVA shows that the manufacturer itself recognizes that AVA is an IND subject to the consent requirements of 10 U.S.C. § 1107. The tacit recognition of AVA's true status as an IND by Bioport, as well as by DoD, is also evidenced by the total lack of clinical human safety and efficacy testing for protection against pulmonary anthrax. To move beyond IND status, clinically verified human testing is required. Here, there has been no human testing, and thus federal statutes and case law, all point to the inescapable determination that the AVA is an IND, and the District Court correctly determined that AVA's use on members of the armed forces without their consent, or a presidential waiver, was unauthorized.[1]

VI. The FDA failed to follow the notice procedure required by law.

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[1] To be sure, the injunction has been lifted to allow for emergency use authorization ("EUA") pursuant to 21 U.S.C. §360bbb-3. However the terms of the EUA make very clear that the use is voluntary with no penalty for refusal to take it. This is the same relief that we submit is appropriate here: an order clarifying that the military can administer AVA, but must do so pursuant to 10 U.S.C. § 1107.

The FDA's own regulation, 21 C.F.R. § 601.25, requires a 90-day public notice and comment period for any rule or order the FDA issues. In 1985 the FDA issued a preliminary order providing the required 90 days for public comment, but the matter was apparently dropped by FDA. Eighteen years later (and just eight days after the injunction in this case was issued), the FDA published a final rule and order. But the final FDA order relies on studies which were not even in existence when the proposed rule and order was noticed in 1985. Judge Sullivan was correct in holding that the public was not given a chance to review or comment on the evidence that the FDA proposed to rely on for its final order, a clear violation of the FDA's well- settled rules for promulgating regulations, requiring that the public be able to review and comment on the evidence supporting a final order. Clearly, when the FDA fails to file a final order for eighteen years, and when the final order relies on evidence that was not even in existence when the proposed order was published, the public comment requirement is made a mockery, and a new notice period is required.

VII. The Department of Defense is administering the AVA even though it is aware of the vaccine's lack of tested efficacy.

The Department of Defense itself has on several occasions recognized the legal limits on the military's ability to use the AVA. On May 16, 1985, the Department of the Army issued a Request for Proposals (RFP) No. DAMD17-85-R-0078 for the "Production of a live bacillus anthracis spore vaccine for human use." The first narrative paragraph of the RFP shows the army's belief that the vaccine

available as of 1985 was not effective against inhalation anthrax. The RFP states "there is no vaccine in current use which will safely and effectively protect military personnel against exposure to this hazardous bacterial agent [bacillus anthracis]." Document No. DAMD17-85- R-0078 at page four.

Ten years later, on October 5, 1995, Anna Johnson-Winegar, Ph.D., Director of the Medical Chemical and Biological Defense Research Program of the Department of the Army wrote to Robert Myers, Ph.D., the Chief of

Biologic Products of MBPI, once again recognizing that the anthrax vaccine needed further studies in order to expand the indication for its use to include protection from aerosol exposure.

Once again, the issue here is not whether the military can use this vaccine; the issue rather is whether it can be administered to military personnel without informed consent or a presidential waiver. An IND cannot be used on military personnel without their informed consent or a presidential waiver as required by Executive Order 13139 and 10 U.S.C. § 1107.

VIII. The problems inherent in testing the anthrax vaccine are not unique, but rather are shared by a number of drugs or vaccines intended to combat biological/chemical warfare.

The FDA is well aware of the problems involved in granting an IND when a drug cannot be tested on humans. On October 5, 1999, the FDA issued a Notice of Proposed Rulemaking (NPRM) to change the licensing requirements for biowarfare drugs and vaccines. In testimony before

Congress on November 9, 1999, William Raub, Ph.D., HHS Deputy Assistant Secretary for Science Policy explained that new regulations were needed in the case of investigational drugs intended to counter the "toxicity of chemical, biological, radiological or nuclear substances which could not be tested ethically on humans." Dr. Raub testified that the rules for human testing should be changed to allow testing on animals alone. 21 C.F.R. §§ 126, 314. The military sought changes in FDA regulations which would allow for a drug or vaccine intended to protect against biological warfare to be exempt from the requirement of human testing. In fact, such a rule, the Animal Efficacy Rule ("AER"), was implemented as part of Section 123 of the BioTerrorism Act of 2002 (P.L. 107-188). This is a direct recognition by the FDA, the military, and the Congress that the previous procedures did not allow approval of an investigational drug which could not be tested on humans. Moreover, the AER is not pertinent to this case, because neither DoD nor BioPort has sought to rely on the AER in their applications, nor was the AER mentioned by the FDA in its putative Order of 2004. Far from relying on the AER to seek animal-only approval, the defendants herein have continued to rely on the flawed and outdated Brachman human study. As argued elsewhere in this brief, and quite aside from the fact that the 2004 order was nearly 20 years late, these data are inadequate to support approval of the AVA.

IX. With regard to drugs such as the anthrax vaccine, it is the civilian government, and not the military, which has ultimate responsibility for the safety of U.S. troops.

FDA, as the pertinent civilian agency, cannot in practical terms cede authority over its vaccine approval process to DoD.

Existing law, which was being ignored until Judge Sullivan issued the injunctions at issue, addresses the situation that may arise when a disease is so deadly that human trials are not ethical. If the circumstances warrant the finding that human testing should be waived, the waiver should be explicit. 10 U.S.C. § 1107 and Executive Order 13139 outline the procedures which must be followed when national security requires administering an investigational drug to military personnel.

In addition, the provisions of 21 C.F.R. § § 50,312 (April 1, 2004) support both the federal statute and the Executive Order by specifically noting situations where the informed consent requirements. may be waived. Echoing 10 U.S.C. § 1107, these regulations state that only the president of the United States may waive the informed consent requirements mandated by his Executive Order and federal law. Such a waiver may be granted only if one of three preconditions is met: obtaining informed consent is not feasible; obtaining informed consent is contrary to the best interests of the recipient; or, informed consent is contrary to national security interests. The President has yet to issue any such waiver.

Under defined procedures set out by law, an investigational drug can be administered without informed consent only if the Department of Defense "can justify to the president" that "need for a waiver of informed consent" is "absolutely necessary." As of the

present day there has been no order from the president that the anthrax vaccine, although investigational, is "absolutely necessary" to the armed forces of the United States and may be administered without informed consent. It is simply illegal, to proceed with a mandatory anthrax vaccination program without complying with 10 U.S.C. § 1107, 21 C.F.R. §§ 50, 312 (April 1, 2004), and Executive Order 13139.

X. The injunction should apply to both the named plaintiffs and all third parties who are affected by the unlawful use of AVA on military personnel.

As discussed above, the use of AVA without informed consent or a presidential waiver is unlawful. Therefore, the injunction here should protect both the Plaintiffs and all other persons affected by the Department of Defense's involuntary anthrax immunization program. Government-wide injunctive relief for both the Plaintiffs and all similarly situated individuals is appropriate and in keeping with case law from this and sister circuits providing injunctive protection to both named parties and other affected third parties. *National Mining Ass 'n, v. U.S. Army Corps of Engineers,* 145 F.3d 1399, 1409 (D.C. Cir. 1998); *Evans v. Harnett County Rd. of Educ.*,684 F.2d 304 (4th Cir. 1982); *Meyer v. Brown & Root Construction Co.,* 661 F.2d 369 (5th Cir. 1981). The Supreme Court has validated this approach. *Lujan v. National Wildlife* Federation, 497 U.S. 871, 890 n.2 and 913 (Blackmun, J. dissenting) (1990). There simply is no requirement limiting injunctive relief to named parties. If an unlawful practice is to

be enjoined, the relief rightly should extend to affected third parties.

CONCLUSION

The preliminary injunction was correct in that at the time the preliminary injunction was issued, there was no final rule in existence, and Bioport and the military themselves had recognized that the anthrax vaccine was an IND. As to the subsequent permanent injunction, it should be upheld because the FDA issued a final rule and order licensing AVA just eight days after the preliminary injunction was issued, but this final order did not come until some eighteen years after the required 90-day comment period on the proposed rule and order. Moreover, the final order relied on data that was not even in existence during the 90-day comment period in 1985, so as a direct result of the FDA's unusual and improper handling of this license application, there was no true opportunity for meaningful public comment on the final rule. The FDA's own regulation, Section 601.25, requires a meaningful comment period, which means a comment period in which the public gets a chance to comment on the evidence and data that the agency will use to justify a final order. Because of the eighteen-year delay and the FDA's reliance on new evidence created after the comment period, the final rule was not a logical outgrowth of the proposed rule, and therefore is not valid. See American Water Works Assoc. v. EPA, 40 F.3d 1266, 1274 (D.C. Cir. 1994).

In addition, there have been no clinical trials on humans, and such trials cannot ethically be

conducted. FDA has recognized that such situations mandate IND status, and FDA has proposed but not finalized a change in the rules allowing for final approval based on animal-only testing. There should be no debate that in such circumstances: 10 U.S.C. § 1107 still applies.

Moreover, on the issue of the propriety of extending the injunctive protections beyond just the plaintiffs here, government-wide injunctive relief for plaintiffs and all individuals similarly situated can be entirely appropriate and it is "well-supported by precedent, as courts frequently enjoin enforcement of regulations ultimately held to be invalid." Sanjour v. United States EPA, 7 F. Supp. 2d 14, 17 (D.D.C. 1998). Therefore, the court was correct in enjoining the use of AVA for all military personnel. Unless and until AVA is properly classified as safe and effective by the FDA for inhalation anthrax, the vaccine remains an IND, and the injunction should remain in effect to require that the use of AVA on both the named plaintiffs and all military personnel conform to the requirements of 10 U.S.C. § 1107. The military is free to use the vaccine, but either must seek the informed consent of vaccine recipients, or must secure a presidential waiver making the vaccine mandatory for military personnel. The preliminary injunction was correct and the permanent injunction must stand.

Dated: August 11, 2005

AMICUS CURIAE
STATE OF CONNECTICUT

_____/s/_____
RICHARD BLUMENTHAL
ATTORNEY GENERAL